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The American Heart Journal

VOL. 14 OCTOBER, 1937 No. 4

Original Communications

FACTORS AFFECTING VASCULAR TONE*

WALTER B. CANNON, M.D.
BOSTON, MASS.

THE honor of giving the first of the George E. Brown Memorial Lectures I appreciate highly. Although my ways and the ways followed by Dr. Brown crossed at many points, it happens that I never had the privilege of meeting him. It would have been a privilege, indeed, for he had many experiences which were related to mine and which would have led, I am sure, to a stimulating exchange of ideas.

As a young man he had his interneship in a small railroad hospital in northern Minnesota. For ten years he practiced medicine in a community of about 10,000 people in Montana. Those were conditions for knowing many kinds of human beings—trainmen, ranchers, cowboys, and the families of a newly settled country. The quality of the man is revealed better than in any verbal testimony by his being among the first in Montana to utilize the tuberculin test, the Wassermann reaction, and the fluoroscope. It is revealed also by his repeated resort to eastern centers for special studies which would render him more useful to those whom he served.

In 1921 his eagerness to contribute to the progress of medicine, besides being a helpful physician, led him to accept a position at the Mayo Clinic. There he continued in activity for nearly fifteen years. During that period his name became known widely through his own country and abroad because of his important contributions to our knowledge of blood vessels and their disorders. His bibliography includes a list of 140 papers, the great majority of which were devoted to studies of vascular disease. It is of interest that as early as 1923 he reported on a case of malignant hypertension, and in the years which followed he and other members of the Division of Medicine at the Mayo Clinic described numerous other cases and observations related to disorders of the circulatory system.

*George E. Brown Memorial Lecture.
Delivered before The American Heart Association, June 7, 1937, in Atlantic City, N. J.

Dr. Brown impressed his associates by the variety of his interests, by his vivid and alert intelligence, his attention to new developments in medicine, his open-mindedness, and by his generous and stimulating attitude toward younger men with whom he came in contact. As someone has remarked, "Dr. Brown beautifully exemplified the glory of the medical guild—the desire to share not only with the community but with all of his fellows the best of his mind, his heart, and his personality." It is in a tribute to him that we gather here today to consider problems which were central in his thought.

The accidental discovery of vasoconstrictor nerves by Claude Bernard in 1851, the prompt confirmation of that discovery by Brown-Sequard and Waller, and Bernard's demonstration of vasodilators in the submaxillary gland brought two new concepts into our understanding of the circulation of the blood. The first was the idea that the blood vessels are under control of the nervous system and therefore can be made to contract or relax and thus vary the resistance of the flow in their channels. The second idea was that the circulation can be adapted to the general requirements of the organism as a whole and also to local needs of particular organs, in accordance with variations of rest or activity. From the earliest observations on the rabbit's ear and on the salivary glands, seventy or eighty years ago, until the recent studies on carotid sinus reflexes and conditions producing hypertension, much of the interest in the physiology of the circulation has been concerned with the factors which affect the distribution of blood in the body.

For many decades studies on the control of blood vessels were fairly simply related to examination of the effects of severing the nervous connections at various points and noting what occurred, or in stimulating severed nerves in order to observe the consequences. The local reflexes of Lovén, the axon reflexes of Langley and the antidromic impulses elucidated by Stricker[1] and Bayliss[2] were revelations of significant new facts pertinent to vascular physiology. These researches on the effects of nervous agencies alone, however, have been complicated by later evidence for humoral or chemical factors which play a rôle in determining the contraction or relaxation of peripheral vessels.

To cover the entire field of the physiology of peripheral blood vessels would be obviously too great a task for a brief lecture. Much that one might say in these circumstances must be set aside, and only certain features of the vascular aspects of circulatory physiology can be considered. In the short time available I propose to consider some of the newer testimony regarding vascular tone. In using the term "vascular tone" I do not commit myself to any particular idea of the nature of the tonic state in smooth muscle or in capillary endothelium. I am using the term to designate a state of moderate contraction of the elements

in the vascular walls—a state which can be both increased and decreased by the operation of appropriate agencies. I am assuming, furthermore, that the discussion will relate only to changes in the blood vessels, i.e., that, unless otherwise specified, we may consider the cardiac pump as engaging in a steady performance. With these provisions declared, I propose that we consider together certain factors which affect the size of vascular channels and thereby produce hypotension, hypertension, and local adjustments of the circulation in accordance with local needs.

THE EFFECTS OF SYMPATHECTOMY ON VASCULAR TONE

In experiments on dogs, Goltz[3] was first to show that severance of the vasomotor nerves left a moderate state of contraction in the blood vessels. This gradually increased and, as judged by temperature, might later more than equal the original degree. The recovery of the contracted state was noted also by Dale and Richards[4] in the vessels of the cat's limb, the nerves of which had been cut; after initial loss of tone there was fairly rapid restoration. Furthermore, Grant and Bland[5] reported a return of the tonic contraction in the vessels of the rabbit's ear after the vasoconstrictor nerves had been cut.

These observations on vascular behavior after denervation in special regions of the body are in harmony with observations made on animals completely deprived of the sympathetic system. In 1931 Bradford Cannon[6] reported records of blood pressure of dogs from which the sympathetic chains had been removed in parts until there were left no connections between the blood vessels and the central nervous system. The sympathetic chains were extirpated in three stages: first, the lumbar sections with severance of the right splanchnics; second, removal of the right thoracic section; and finally, the left thoracic section with the left splanchnics. An immediate fall of arterial pressure occurred after completion of each stage. When the final portion of the sympathetic was taken, the pressure, after the primary drop, came to rest somewhat lower than the original level, i.e., at about 120 mm. Hg.

The blood pressure of the dogs studied by Bradford Cannon was measured by means of a pressure cuff and auscultation or palpation. The fairly normal pressure which he noted after extirpation of the last segment of the sympathetic system was confirmed for cats as well as for dogs by Bacq, Brouha, and Heymans.[7] They measured the arterial pressure by connecting the femoral artery with a mercury manometer. In totally sympathectomized animals they state that the recovery from low pressure is by way of a progressive return. Further evidence regarding the restoration of pressure in animals wholly deprived of the sympathetic system was reported by Wilson, Roome, and Grimson[8] last year. Again the return of a fairly normal blood pressure was noted. The evidence is clear from all these studies that, just as peripheral vascular tone is restored locally after local section of vasoconstrictor

nerves, there is a corresponding restoration of tone and a consequent persistence of a fairly normal arterial pressure after the sympathetic system has been entirely extirpated.

Thus far the return of normal pressure after sympathectomy has been explained as due solely to the recovery of a tonic state in the vascular walls. Conceivably the recovery is not complete. In that case the return might be aided by an increase of blood volume—an increase which would compensate for a greater capacity in the circulatory system. In studies on dogs Wilson, Roome, and Grimson[8] came to the conclusion that the quantity of circulating blood is not greater after complete sympathectomy than before. Their estimates were based, however, on the bleeding volume. It is questionable whether that method can yield satisfactory evidence. In the normal animal reflex vasoconstriction occurs as the blood pressure falls, and thus blood would be forced out of the vessels until the last heartbeat. In the sympathectomized animal reflex reduction of the vascular capacity cannot occur, and, therefore, a bleeding volume after sympathectomy *equal* to that in normal animals, might reasonably be interpreted as indicating a more than normal amount of blood in the vessels. There is some evidence that the blood volume is indeed greater after sympathectomy than before. Hamlin, in unpublished observations on sympathectomized cats, has found (in seven animals) that the average increase of the quantity of circulating blood was 25 per cent. His estimates were based on the use of Gregersen's well-tested blue-dye method. Four or five measurements were made before the operation and a similar number afterwards. The animals had all regained their former weight before the postoperative determinations were made. Curiously the determinations after removal of the sympathetic fibers showed wider variations than those made before. These are data which must be confirmed; they indicate, however, that the restored blood pressure after sympathectomy may be partially due to a larger amount of blood filling a more capacious system.

Condition Affecting Physiological Tone After Sympathectomy.—Since the observations of Meltzer and Auer[9] in 1904, it has been recognized that section of the sympathetic nerves supplied to smooth muscle renders the muscle more sensitive to adrenalin or secreted adrenine. Their observations were made on the blood vessels of the rabbit's ear and also on the cat's iris and nictitating membrane. These facts have been repeatedly confirmed by other observers and have been extended to smooth muscle in other parts of the body. About two years ago Hampel[10] reported on the rate of development of sensitiveness as manifest in the smooth muscle of the nictitating membrane. During the first week there is a rapid gain, which is followed by a slower gain during the second week. On the fifteenth or sixteenth day after section of sympathetic fibers a maximal responsiveness is reached and thereafter is maintained. An important consideration related to sensitization to adrenine is the

fact that severance of preganglionic fibers, according to Hampel, results in only approximately half as great sensitiveness to adrenine as that produced by severance of postganglionic fibers. Similar observations, but on blood vessels, have recently been reported by Ascroft.[11] He estimated that after postganglionic section the vessels are about ten times as sensitive as are the controls, and after preganglionic section only three times as sensitive. Attention to this point allows smooth muscle to be separated from the central nervous influences without being rendered especially responsive—a practical matter, the value of which surgeons have recognized.

The importance of sensitization of vascular smooth muscle to circulated adrenine lies in the fact that common conditions in daily life naturally result in a discharge of an extra amount of adrenine into the circulation. This is due to the control exercised by the sympathetic nervous system on the adrenal medulla. In a long series of experiments, carried on for many years in the Harvard Physiological Laboratory, evidence has been secured that emotional excitement, hypoglycemia, cold, pain, and vigorous muscular activity all increase medulliadrenal secretion.[12] These observations have been confirmed by various investigators using a variety of methods and working independently in different parts of the world. The question naturally arises as to whether the tone of blood vessels deprived of sympathetic nerves will be altered by conditions which influence secretion of adrenine.

First, let it be understood that in man, just as in the cat, as Freeman, Smithwick, and White[13] found, smooth muscle—that of the blood vessels of the fingers, for example—becomes more sensitive to injected adrenalin six to eight days after sympathectomy. In this relation it is of considerable interest that the conditions which have been shown to cause an increase of adrenal secretion are precisely the conditions which may affect contraction of sensitized denervated vessels. Thus, contraction of the blood vessels of the sympathectomized ear of the rabbit has been reported by Grant,[14] who charted the fall of temperature of the ear when a leg was held and the animal struggled. Analogously, Grant and Pearson (Grant[14]) have noted that, when a man struggled against resistance for a minute, there was contraction of his denervated blood vessels, indicated by a fall of temperature of the foot through 2° C. Furthermore, Freeman, Smithwick, and White observed that, when a patient became excited, there was a contraction of the denervated vessels. During insulin hypoglycemia, also, there was a striking vasoconstriction. Chilling of the body, which we know induces sympatho-adrenal activity, as shown by gooseflesh, will also cause a narrowing of the denervated vessels, as Freeman[15] has shown. This contraction is not due to direct action on the sensitized vessels, for it appeared when the hands were maintained at a constant temperature while ice bags were applied to both supraclavicular regions. In all these observations on man the experimental

observations on lower animals have been repeated. They definitely offer evidence that excitement, hypoglycemia, cold, and muscular effort cause effective secretion from the human adrenal medulla. Pain would probably have the same influence, though observations on that point have not been made on man. This result of conditions which increase medulliadrenal secretion probably explains anomalies which not infrequently have been reported regarding the return of spasm in peripheral vessels long after they have been deprived of their sympathetic nerve supply.

In the foregoing account the contraction of denervated blood vessels has been attributed solely to adrenal secretion. There is another agent which may have similar effects. That is the substance "sympathin," which is given off at sympathetic nerve endings when there is a discharge of impulses into the effectors. In 1935 Grant[14] reported that after removal of the adrenal glands or the pituitary body the previous reactions of the normal and the denervated ear were not altered. He presented no record of the changes in the denervated ear when the animal was exposed to a reduced temperature, or was made to struggle, after the adrenals had been extirpated, but presumably those tests were applied. Grant admits the possibility that the sensitive vessels were affected by circulating sympathin. It seems probable that this is the explanation of his observations. We know that denervated vessels become sensitized to sympathin just as they become sensitized to adrenine. And White, Okelberry, and Whitelaw[16] have noted an intense blanching of a rabbit's sympathectomized ear when, after removal of the adrenals, they stimulated hepatic nerves—a mode of liberating sympathin which is highly effective. We have learned that sympathin is discharged into the blood stream under the same conditions as adrenine and that ordinarily sympathin and adrenine collaborate in producing changes in sympathetic effectors. It is quite possible, however, that sympathin may alone produce these changes.

The fact that activity of the sympathetic system provokes a discharge of both sympathin and adrenine and that these two agents can work together to influence regions which have been deprived of their sympathetic nerves[17] raises the question as to whether the recovery of tone in vascular smooth muscle may not be due to the continued presence of a small amount of these substances in the blood stream. According to Sataké, Sugawara, and Watanabé,[18] there is a discharge of adrenine from the adrenal medulla, even in the most quiet conditions, amounting to 0.00007 milligram per kilogram of body weight per minute. There is a bare possibility that this extremely small amount may have been due to the manipulation incident to taking the blood sample required for the estimate, though great care was used to avoid disturbance of the animal. In experiments on cats with denervated hearts I was

unable to find any difference between the heart rate in the animals completely at rest and with intact adrenals, and the same animals after the adrenal glands were rendered wholly inactive. Since the denervated heart is an extraordinarily sensitive indicator of adrenal secretion it would appear that the amount of adrenine produced in complete rest is probably not enough to have any influence on vascular tone.

Whether there is another gland of internal secretion—for example, the posterior lobe of the pituitary or the adrenal cortex—which supplies a chemical agent that might account for the restoration of tone in sympathectomized vessels is not known. Certainly if endocrine organs are effective agents in reestablishing the tonic state they are not called into action by the discharge of impulses through sympathetic pathways, for in completely sympathectomized animals those pathways are absent. There is no indication, however, that any gland of internal secretion is necessary for the development of tone in smooth muscle—certainly not the adrenal medulla. That statement is supported by observations on the alimentary tract. Many years ago I isolated the stomach from the central nervous system.[19] The smooth muscle of this organ is *relaxed*, not contracted, by adrenine. And yet, after a short time, the denervated muscle of the gastric wall shows an almost incredible degree of tonic contraction. Until definite proof that an external agent operates to restore "tone" in denervated vascular muscle I believe we are warranted in assuming that the restoration results from an intrinsic property of the muscle itself.

In connection with variations of tone of denervated blood vessels, the interesting reports from Freeman, and Freeman and Zeller on the effects of heat and cold on the circulation rate may be mentioned. In observations on patients Freeman[15] found a remarkably close relationship between the volume flow of blood in a sympathectomized hand and the metabolic rate. When the rate was increased or decreased by placing the hand in warm or cold water the volume flow was correspondingly altered. In unpublished observations Freeman and Zeller have confirmed these data in experiments on totally denervated paws of unanesthetized trained dogs in which one adrenal had been removed and the other denervated. Again the circulation varied with the temperature of the bath in which the paw was immersed. The conclusion was drawn that the blood supply through regions deprived of vasomotor control might be determined by the metabolic needs of the tissues. Although not denying that possibility and deferring until later a consideration of the way in which metabolites may influence blood flow, I may mention that Freeman has recognized that smooth muscle contracts when exposed to cold and relaxes when exposed to warm surroundings, and that therefore the variations in blood flow which he observed might be the consequence of temperature changes in the vessels themselves.

ADAPTATION OF VASCULAR TONE TO LOCAL NEEDS

The evidence relative to changes of vascular tone in accordance with the quiescence or the activity of organs has been derived chiefly from studies on muscle. The classic experiments of Krogh[20] showed that when the muscles of a guinea pig are made to contract the number of capillaries which are visibly relaxed and containing blood may be more than ten times the number visible in the resting muscle, and in the frog the increase may be nearly fortyfold. The early observations by Chauveau and Kaufmann (see Kaufmann[21]) revealed an increased blood flow through rhythmically active muscles which might be as much as five times the amount passing through the same muscles when at rest. These results have been confirmed by other investigators, notably by Barcroft and Kato[22] who pointed out that the increase occurred as an aftereffect of contraction.

The most recent and apparently the most reliable studies of this phenomenon are those of Anrep,[23] who used a hot-wire anemometer to record the blood flow. By means of this device he was able to show that a tetanic contraction, whether reflex or induced by stimulation of a motor nerve, causes the flow through the muscle to be greatly reduced and may actually stop it. After the contraction, however, it is much increased. If the muscle contracts rhythmically the flow becomes gradually more ample between successive contractions until a maximum is reached. The greater supply of blood depends upon the strength of the contraction. It would appear that the observation, well known since the report by Roy and Brown[24] nearly sixty years ago, that arrest of the circulation is followed by a considerably augmented flow through vessels in which the flow has been checked, may be a phenomenon similar to that seen in active muscles. The phenomenon noted by Anrep, however, is not solely due to a check on the circulation during the contractile phase, for he found that if blood is forced through muscles during their contraction it acquires the property of causing a reduction of vascular tone. Obviously some agent is produced by the activity of the muscle itself that has the observed effect.

For our present interests the question that becomes prominent is that of explaining the increased circulation when skeletal muscle fibers contract and shut off their own blood supply and simultaneously become the seat of special metabolic processes. Various explanations have been given to account for the dilation of blood vessels in active organs. The demonstration by Gaskell[25] that lactic acid lessens the tone of blood vessels, and Bayliss'[26] testimony that carbon dioxide has the same effect, serve to bring acid metabolites into the picture as possible agents inducing the larger flow. Whether the observation that lack of oxygen (cf. [24]) has a similar influence is to be ascribed directly to that condition or indirectly to the development of an acid reaction is not yet clear. As Anrep has remarked, there has been a tendency, as each new substance

has been discovered, to ascribe to it responsibility for the vasodilator effect in active muscle and in other organs. Histamine, acetylcholine, adenylic compounds and other unidentified substances have in turn been regarded as the cause of the phenomenon. Gaddum[27] has declared that no single substance known to be present in the tissues could account completely for the characteristics of reactive hyperemia, during which there is a dilation of all the vessels. Liberation of histamine could explain dilation of the capillaries but not dilation of the arterioles—the presence of some other agent would have to be assumed to account for effects on these structures. Possibly the early testimony of Gaskell and Bayliss regarding the action of acids may be most pertinent, for Rous and Drury[28] have shown by direct observation a considerable local increase in the hydrogen ion concentration in ischemic tissues—an increase which under certain conditions might control the blood flow. It is unfortunate that we have no decisive evidence regarding the agencies which adapt the tone of the blood vessels, and thereby the flow of the blood, to the needs of organs as they vary between rest and activity.

THE QUESTION OF INHIBITORS OF VASCULAR TONE (I.E., VASODILATOR NERVES)

In discussing inhibition of vascular tone I am not concerned with the depression of activity of the vasoconstrictor center, but instead I wish to take up the pros and cons of the existence of a vasodilator center which produces vasodilation by relaxing smooth muscle. That smooth muscle may be relaxed by nerve stimulation is common knowledge. The relaxation of the stomach and intestines, and likewise the nonpregnant uterus of the cat, when sympathetic impulses are delivered, are noteworthy instances. It would not be strange, therefore, to find nerve impulses which would relax the smooth muscle of blood vessels by inhibiting their tonic state. Nevertheless, Barcroft[29] has argued that the dilation of the blood vessels of the submaxillary gland, for example, when the chorda tympani is stimulated, is due to the action of metabolites set free from the gland and therefore "the hypothesis of dilator fibers in the chorda of the cat seems superfluous." That argument cannot hold, however, in the effects of stimulating the *nervi erigentes* where metabolites are not produced which could dilate the vessels.

The interest of the Harvard Physiological Laboratory in vasodilator nerves was stimulated by the remarkable behavior of sympathectomized cats. The observation was repeatedly made that if these sympathectomized animals engaged in any vigorous activity they promptly collapsed. When Freeman and Rosenblueth[30] measured blood pressure at the time of a vigorous struggle the fact appeared that the pressure instead of rising, as it does in normal animals, actually fell. Similar observations have been made on dogs. For a period of some days after

the completion of sympathectomy Freeman[31] found that there was so great a drop of pressure when an animal was vigorously exercised that fainting occurred. Later the dog recovers and is able to endure strenuous muscular exertion without the disturbing effects seen in the cat.[32] Nevertheless, as Pinkston, Partington, and Rosenblueth[33] have demonstrated, muscular activity causes some fall of blood pressure even in the dog well recovered from the operation of sympathectomy.

The observations just described have been given different interpretations. Bacq, Brouha, and Heymans[7] have claimed that the fall of pressure is due to muscular metabolites which, as we have seen, are capable of causing a dilation of the blood vessels. In support of this view they found that the addition of carbon dioxide to the air breathed by a sympathectomized cat caused a fall of arterial pressure. It also caused, however, a greatly increased respiratory rate, and the possibility exists, therefore, that the changed conditions brought about by excessive respiration might have produced the effect. Furthermore, there is chance that the excess of carbon dioxide might stimulate a vasodilator center and thereby induce a fall of pressure. It would appear reasonable also that if muscular metabolites are the essential cause of a lowered pressure in sympathectomized animals the dog might be expected to suffer as much as the cat. The effect, though present in the dog, is not so striking as in the cat. The difference between the two species may be attributed to a greater efficacy of vasodilator nerves in the cat. Furthermore, the fall of blood pressure in sympathectomized, vagotomized animals when they struggle starts almost immediately—apparently much too soon to be readily explained by the metabolites resulting from muscular contraction. Also, when the peripheral end of the cut sciatic nerve is stimulated in a sympathectomized cat there is first a rise of blood pressure, as might be expected from Anrep's observations on the effects of muscular contraction, and a fall occurs only after the stimulus ceases. Neither in the cat nor in the dog is struggle associated with this initial rise of pressure. From all these lines of evidence it seems clear that the explanation of the drop in the blood pressure record is not well explained by the development of metabolites alone.

Bacq, Brouha, and Heymans have suggested that there may be nonsympathetic vasoconstrictor nerves and that the fall of pressure in animals deprived of the sympathetic system may result from a block of constrictor impulses. The evidence cited by them was based on the effect of one milligram of percain, injected into the spinal canal in the cervical region. This drug, they assumed, produced a "physiological section" of the spinal cord. The consequent drop of arterial pressure they attributed to the action of the drug in eliminating tonic vasoconstrictor impulses. When, instead of using a drug, however, Rosenblueth and I[34] made a true section of the cord in the cervical region and found that it did not modify the pressure of sympathectomized cats, we felt

justified in dismissing as inconclusive the evidence obtained by the Belgian investigators. Our view was confirmed by the observations of Wilson, Roome, and Grimson,[8] and also of Bradshaw[35] that novocaine spinal anesthesia, which dropped the blood pressure of normal animals, had no hypotensive influence on the sympathectomized. Another argument in favor of nonsympathetic vasoconstrictors, which was advanced by Bacq, Brouha, and Heymans, was based on the observation that hypotension in the carotid sinus caused arterial hypertension in the sympathectomized animal. This observation was not confirmed by Thomas and Brooks,[36] however, and likewise not confirmed by Pinkston, Partington, and Rosenblueth.[33] The main reason for giving credit to this accumulation of negative evidence is that Bacq, Brouha, and Heymans do not mention excluding the possibility of regrowth of nerves to the celiac ganglion and the adrenals. As was shown by Bacq and Dworkin,[37] such regrowth may occur, and unless scrupulous care is given to this possibility it may lead to highly confusing results. The weight of evidence favors the view that nonsympathetic nervous influences on the blood vessels are not of vasoconstrictor type.

That it is possible to obtain true vasodilation, i.e., relaxation of vascular tone, in sympathectomized animals by nervous influences acting directly on the vessels, was shown by Rosenblueth and myself[34] in 1934. We made use of Ranson and Billingsley's observation[38] that there are on each side of the floor of the fourth ventricle two well-separated points, stimulation of which causes alteration of blood pressure—the anterior points causing a rise and the posterior a fall. In sympathectomized animals we found that stimulation of the depressor points consistently elicited a fall of blood pressure. We were careful to place the electrodes properly and use threshold stimuli so that there was no attendant muscular movement. The depressor effect was not eliminated by the exclusion of the splanchnic area, for it persisted after the aorta was clamped at the level of the diaphragm. Stimulation of neighboring regions, including the pressor points, did not alter the arterial pressure unless the current was sufficient to induce muscular activity. Then there was an initial rise succeeded by a fall just as when a peripheral nerve is excited.

The experiments of Pinkston, Partington, and Rosenblueth,[33] moreover, brought forth definite evidence that in both the sympathectomized dog and the cat central stimulation of vagus and depressor nerves would cause a distinct fall of blood pressure. In all cases there were no changes of activity except in respiration; and the respiratory change was definitely ruled out as the occasion for the depressor effect. In the sympathectomized cat central stimulation of the brachial nerve, for example, repeatedly produced striking drops of the pressure level. Muscular movements which might be induced by spinal reflexes were eliminated in some instances by section of the efferent nerves which were

involved. These sections altered slightly the magnitude but not the downward direction of the blood pressure response. The results, noted in the sympathectomized cat, were obtained also in experiments on sympathectomized dogs.

The existence of a vasodilator center, the activity of which is reciprocally related to a vasoconstrictor center, was inferred by Bayliss[39] in 1908, for he found that when constrictor impulses were eliminated from a given vascular region by severing its sympathetic fibers, reflexes which involved vasodilation were still effective in causing an enlargement of these sympathectomized vessels. Earlier, Bayliss[2] had reported experiments which revealed the possibility of vasodilator influences in the limbs that might be mediated through the dorsal roots. The phenomena observed in 1913 by Fofanow and Tschalussow[40] and later by Bishop, Heinbecker, and O'Leary[41] and also by Tournade and Malméjac,[42] showed that the vasodilator fibers of the dorsal roots could be activated reflexly. It seems probable, therefore, that in sympathectomized animals these are the efferent pathways of the impulses which cause an inhibition of peripheral tone. They would be, then, responsible for that drop of blood pressure which attends struggle, which follows stimulation of depressor points in the floor of the fourth ventricle, and which results reflexly when afferent nerves are excited.

CONDITIONS PRODUCING EXCESSIVE VASCULAR TONE

As is well recognized, the height of arterial pressure depends upon the energy of the output from the heart as related to the resistance to the onward passage of blood into the capillaries. A condition of hypertension, other things equal, depends chiefly on the resistance offered to the blood flow in the finer divisions of the arteries, the arterioles. In such circumstances, with a marked vasoconstriction in that part of the circulatory system, a heightened blood pressure will result. The persistent state of hypertension which develops pathologically in certain individuals presents an important physiological and medical problem. Unfortunately the condition may become so severe—the pressure may rise so high—that life may be endangered; then the adjective "malignant," applied to it, is fully justified.

Three explanations of the hypertensive state in the arterioles could theoretically be possible. It might result from excessive discharge of vasoconstrictor impulses from the central nervous system, such as to induce an abnormal narrowing of the channels. Or it might be due to increased sensitiveness of the smooth muscle of the arterioles to natural stimuli which cause contraction. Or these small vessels might be pathologically constricted because of direct action upon them of unusual chemical agents. We now have, in fact, evidence that each of these conditions may produce an augmented vascular contraction. We shall consider them in the order mentioned.

1. The studies of Heymans and his collaborators have furnished evidence that if all the restraining nerves are severed—the cardio-aortic nerves (depressor) and those of the carotid sinus as well—there develops a hypertension which persists for an indefinite period. Heymans and Bouckaert[43] have reported long-continued observations on a single animal, a dog. Before section of the restraining nerves the arterial pressure was approximately 140 mm. Hg, and the cardiac rate 90 beats a minute. After section of these nerves the pressure rose promptly to 240 mm. Hg, and thereafter went up gradually until after eight months it reached 300 mm. The heart rate likewise rose until it ran about 300 beats a minute. After sixteen months, when the arterial pressure was about 270 mm. Hg, the abdominal sympathetic strands as well as the splanchnic nerves were severed. Arterial pressure, after being reduced for some days immediately after the operation, stabilized between 280 and 300 mm., i.e., there was no improvement. The heart, however, which had begun to beat more slowly, continued toward the previous normal level.

About the twenty-fifth month, i.e., after two years of high pressure, the celiac plexus was removed. Then there was a marked and lasting fall of the pressure which stabilized at about 200 mm. Hg. It may be that there had been a regrowth of splanchnic (preganglionic) fibers into the celiac ganglion—a possibility already noted—and that the persistence of high pressure was partly due to that. On the other hand, the rise, a short time after excision of the abdominal sympathetic strands and section of the splanchnics, might be explained as a consequence, to some degree, of independent activity of the outlying neurones in the sympathetic system, i.e., those of the prevertebral ganglia. That explanation would be in harmony with the observations of Govaerts,[44] whose experiments indicated that the stellate ganglion, disconnected from the central nervous system, becomes after some days independently active and the source of a cardio-accelerator tone.

The dog studied by Heymans and Bouckaert did not have a restoration of normal pressure until both thoracic sympathetic chains were removed, in addition to the removal of the abdominal chains. When these final operations were completed, after 27 months, the arterial pressure was restored to its former level. The Belgian investigators have drawn the conclusion that when hypertension is brought about by removal of the restraining nerves the consequent persistently high arterial pressure is abolished only when there is complete removal of the sympathetic strands, and, in addition, an excision of isolated sympathetic ganglia such as the celiac. They especially emphasize the possibility that these ganglia, even when disconnected from the central nervous system, may become centers of vasoconstrictor tone. Unfortunately their conclusions are based on a single experiment, and that one not critically performed.

The experiment is, however, of the sort which should be performed. Because of the importance of the inferences drawn from it, it should be carefully repeated.

2. That some blood vessels, even though innervated, may become especially sensitive to natural stimuli was shown by Lewis[45] and by Heinbecker and Bishop,[46] in studies on patients with Raynaud's disease. Lewis noted that when cold was locally applied to an affected finger there was local vasospasm without general involvement of the sympathetic system. And Heinbecker and Bishop observed that adrenine, whether subcutaneously injected or secreted in response to hypoglycemia, produced exceptionally emphatic constriction in the vessels of abnormal digits. They also adduced evidence that these vessels were peculiarly overresponsive to normal sympathetic impulses; since these impulses liberate sympathin, however, and that substance closely resembles adrenine, the effect is what might be expected.

In all these cases the disease had reached an advanced stage. White,[47] (p. 163) has presented arguments which would attribute the phenomenon of local sensitiveness to the pathology which develops at that stage and would explain the early appearance of spasm in Raynaud's disorder to hyperactivity of vasoconstrictor nerves.

3. The third way in which dangerous vasoconstriction might develop is through peripheral stimulation of the smooth muscle of the arterioles by unusual chemical agents. Naturally one thinks, first, of such natural agents as pituitrin and adrenine, both of which are capable of causing contraction of smooth muscle. In acute experiments, however, pituitrin does not have a persistent effect in contracting vascular muscle—successive doses become less effective than the first. Furthermore, Grant has shown that vascular tone develops in the absence of the pituitary gland. Since we have experimental proof that the adrenal medulla does not secrete unless it is stimulated by nervous impulses (or in the rare condition of extreme asphyxia), the idea that secreted adrenine plays a rôle in producing excessive constriction of the arterioles must, I believe, be abandoned.

The most illuminating indication that persistent hypertension is induced by some chemical agent, apparently other than that put forth by one or more of the glands of internal secretion, has come from the important experiments of Goldblatt and his collaborators.[48] I hesitate to expound the evidence developed from these experiments because a paper which is to be given this afternoon will clearly bring out the facts. The most interesting point in relation to the present discussion, however, is that Freeman and Page have been able to demonstrate that reduction of the blood flow through the kidneys by application of Goldblatt's clips causes hypertension in animals which have been completely sympathectomized. Or if hypertension has been produced by partial ischemia of the kidneys, subsequent sympathectomy does not improve the situation. These observations appear to place the action in some

agent which affects vessels at the periphery. There is, however, the bare possibility that the hypothetical agent might influence primarily prevertebral ganglia such as the celiac and the inferior mesenteric, and by exciting these isolated groups of cells, which constrict the splanchnic vessels, might be the occasion of the hypertensive state.

We have now surveyed briefly recent studies on the effects of sympathectomy on vascular tone, the conditions which affect vascular tone after sympathectomy, the adaptation of vascular tone to local needs of the tissues, the question of inhibitors of the tonic state in blood vessels, and the conditions which may produce excessive vasoconstriction. Unfortunately time has not been available for discussion of the factors which influence specifically the functional adjustments of the capillaries. That subject will remain for some future lecturer to consider, who comes before you to refresh the memory of George E. Brown, and his services to the physiology and pathology of the circulatory system.

REFERENCES

1. Stricker, S.: Untersuchungen über die Gefässnervenwurzeln des Ischiadicus, Sitzungber. d. k. Akad. d. Wissensch. Math.-naturw. kl. Wien **74**: 173, 1876.
2. Bayliss, W. M.: On the Origin From the Spinal Cord of the Vaso-dilator Fibres of the Hind-Limb and on the Nature of These Fibres, J. Physiol. **26**: 173, 1901. And, Further Researches on Antidromic Nerve Impulses, Ibid. **28**: 276, 1902.
3. Goltz, Fr.: Über gefässweiternde Nerven, Arch. f. d. ges. Physiol. **9**: 174, 1874.
4. Dale, H. H., and A. N. Richards: The Vaso-dilator Action of Histamine and Some Other Substances, J. Physiol. **52**: 110, 1918.
5. Grant, R. T., and Bland, E. F.: Observations on the Vessels and Nerves of the Rabbit's Ear With Special Reference to the Reaction to Cold, Heart **16**: 69, 1932.
6. Cannon, B.: The Effects of Progressive Sympathectomy on Blood Pressure, Am. J. Physiol. **97**: 592, 1931.
7. Bacq, Z. M., Brouha, L., and Heymans, C.: Reflexes vasomoteurs d'origine sino-carotidienne et actions pharmacologiques chez le chat et chez le chien sympathectomisés, Arch. internat. de pharmacodyn. et de thérap. **48**: 429, 1934.
8. Wilson, H., Roome, N. W., and Grimson, K.: Observations on Certain Vascular Reactions During and After Complete Exclusion of the Sympathetic Nervous System in Dogs, Ann. Surg. **103**: 498, 1936.
9. Meltzer, S. J., and Auer, C. M.: Studies on the "Paradoxical" Pupil-Dilatation Caused by Adrenalin, Am. J. Physiol. **11**: 28, 1904.
10. Hampel, C. W.: The Effect of Denervation on the Sensitivity to Adrenine of the Smooth Muscle in the Nictitating Membrane of the Cat, Ibid. **111**: 611, 1935.
11. Ascroft, P. B.: The Basis of Treatment of Vasospastic States of the Extremities, Brit. J. Surg. **24**: 787, 1937.
12. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear, and Rage, New York, 1929; and the Wisdom of the Body, New York, 1932.
13. Freeman, N. E., Smithwick, R. H., and White, J. C.: The Reactions of the Blood Vessels of the Human Extremity, Sensitized by Sympathectomy, to Adrenalin and to Adrenal Secretion Resulting From Insulin Hypoglycemia, Am. J. Physiol. **107**: 529, 1934.
14. Grant, R. T.: Further Observations on the Vessels and Nerves of the Rabbit's Ear, With Special Reference to the Effects of Denervation, Clin. Sc. **2**: 1, 1935.
15. Freeman, N. E.: The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, Am. J. Physiol. **113**: 384, 1935.
16. White, J. C., Okelberry, A. M., and Whitelaw, G. P.: Vasomotor Tonus of the Denervated Artery, Arch. Neurol. & Psychiat. **36**: 1251, 1936.
17. Cannon, W. B., and Rosenblueth, A.: Autonomic Neuro-effector Systems, New York, 1937.

18. Sataké, Y., Sugawara, T., and Watanabé, M.: A Method of Collecting the Blood From the Suprarenal Gland in the Dog, Without Fastening, Narcotizing, Laparotomy, or Provoking Any Pain, Tohoku J. Exper. Med. **8**: 501, 1927.
19. Cannon, W. B.: The Motor Activities of the Stomach and Small Intestine After Splanchnic and Vagus Section, Am. J. Physiol. **17**: 429, 1906.
20. Krogh, A.: The Anatomy and Physiology of the Capillaries (revised edition), New Haven, 1929.
21. Kaufmann, M.: Recherches expérimentales sur la circulation dans les muscles en activité physiologique, Arch. de Physiol. **24**: 279, 1892.
22. Barcroft, J., and Kato, T.: Effects of Functional Activity in Striated Muscle and Submaxillary Gland, Phil. Trans., Roy. Soc., London, **207 B**: 149, 1916.
23. Anrep, G. V.: Studies in Vascular Regulation, 1936, Stanford Univ. Press.
24. Roy, C. S., and Brown, J. G.: The Blood Pressure and Its Variation in the Arterioles, Capillaries and Smaller Veins, J. Physiol. **2**: 323, 1879-80.
25. Gaskell, W. H.: Über die Aüderung des Blutstroms in den Muskeln durch die Reizung ihrer Nerven, Arb. a. d. physiol. Anstalt, Leipzig **11**: 45, 1876.
26. Bayliss, W. M.: The Action of Carbon Dioxide on Blood Vessels, J. Physiol. **26**: 32, 1901.
27. Gaddum, J. H.: Gefässweiternde Stoffe der Gewebe, Leipzig, 1936.
28. Rous, P., and Drury, D. R.: Outlying Acidosis Due to Functional Ischemia, J. Exper. Med. **49**: 435, 1929.
29. Barcroft, J.: The Mechanism of Vasodilation in the Cat's Submaxillary Gland, J. Physiol. **36**: 53, 1908.
30. Freeman, N. E., and Rosenblueth, A.: Reflex Stimulation and Inhibition of Vasodilators in Sympathectomized Animals, Am. J. Physiol. **98**: 455, 1931.
31. Freeman, N. E.: Personal communication.
32. Brouha, L., Cannon, W. B., and Dill, D. B.: The Heart Rate of the Sympathectomized Dog in Rest and Exercise, J. Physiol. **87**: 345, 1936.
33. Pinkston, J. O., Partington, P. F., and Rosenblueth, A.: A Further Study of Reflex Changes of Blood Pressure in Completely Sympathectomized Animals, Am. J. Physiol. **115**: 711, 1936.
34. Rosenblueth, A., and Cannon, W. B.: A Further Study of Vasodilators in Sympathectomized Animals, Ibid. **108**: 599, 1934.
35. Bradshaw, H. H.: The Fall in Blood Pressure During Spinal Anesthesia, Ann. of Surg. **104**: 41, 1936.
36. Thomas, C. B., and Brooks, C. M.: The Effect of Sympathectomy on the Vasomotor Carotid Sinus Reflexes of the Cat, Am. J. Physiol. **113**: 130, 1935.
37. Bacq, Z. M., and Dworkin, S.: Regeneration of Fibers in the Sympathico-Adrenal System, Ibid. **93**: 629, 1930.
38. Ranson, S. W., and Billingsley, P. R.: Vasomotor Reactions From Stimulation of the Floor of the Fourth Ventricle, Ibid. **41**: 85, 1916.
39. Bayliss, W. M.: On Reciprocal Innervation in Vasomotor Reflexes and on the Action of Strychnine and Chloroform Thereon, Proc. Roy. Soc., London, **80 B**: 339, 1908.
40. Fofanow, L. L., and Tschalussow, M. A.: Über die Beziehungen des N. depressor zu den vasomotorischen Zentren, Arch. f. d. ges. Physiol. **151**: 543, 1913.
41. Bishop, G. H., Heinbecker, P., and O'Leary, J. L.: The Function of the Nonmyelinated Fibers of the Dorsal Roots, Am. J. Physiol. **106**: 647, 1933.
42. Tournade, A., and Malméjac, J.: Mechanisme du réflexe vaso-dilatateur que provoque l'excitation du nerf de Hering, Compt. rend. Soc. de Biol. **112**: 679, 1933.
43. Heymans, C., and Bouckaert, J. J.: Hypertension artérielle chronique expérimentale et sympathectomie, Bull. Acad. roy. de méd. de Belgique, Feb. 29, p. 42, 1936.
44. Govaerts, J.: Apparition d'un tonus cardio-accélérateur dans le ganglion stellaire déconnecté centralment, Compt. rend. Soc. de Biol. **119**: 1181, 1935.
45. Lewis, T.: Experiments Relating to the Peripheral Mechanism Involved in Spasmodic Arrest of the Circulation in the Fingers, a Variety of Raynaud's Disease, Heart **15**: 7, 1929.
46. Heinbecker, P., and Bishop, G. H.: On the Mechanism of Spastic Vascular Disease, Proc. Soc. Exper. Biol. & Med. **32**: 152, 1934.
47. White, J. C.: The Autonomic Nervous System, New York, 1935.
48. Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W.: The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, J. Exper. Med. **59**: 347, 1934.

STUDIES IN THE PATHOLOGY OF VASCULAR DISEASE*

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EVIDENCE concerning the basic processes leading to the formation of atheroma and related vascular changes is presented. This evidence has been obtained by combination and intensive application of known techniques. It is believed the new knowledge aids in the understanding of the anatomical processes involved in atherosclerosis and that this points the way to further study of cause as well as relation of vascular and organ changes in a group of diseases.

The importance of vascular disease in its various manifestations need not be stressed. As a result of rapidly increasing knowledge of diseases of childhood and early maturity and improved measures for their prevention and care, vascular disease and associated organic changes now top the mortality list. Contributions concerning the pathology of the various processes have been disappointing. The etiology is obscure, and the source of the materials, lipoid and otherwise, so characteristic of early atheroma is no clearer, despite many attempts to relate them to diverse maladjustments, especially dietary.

Present-day descriptions of the process differ in no essential from those of Morgagni save that they are more brief and employ a somewhat changed nomenclature. The histological picture and its interpretation is not different from that of the time of Virchow. The description of the typical atheroma, as given in contemporary texts, briefly, is somewhat as follows: The intimal thickening, gray, waxy, or yellow and opaque, bulges into and partially or completely occludes the lumen of the vessel. As the patch, devoid of any vascularity, grows, its deeper part near the media undergoes necrosis since it is far removed from the circulating blood in the lumen, and insulated from the vasa in the adventitia by the media. If this necrosis extends to the surface and involves the endothelium, an atheromatous ulcer develops, with thrombus formation supervening. Vascularity at the margin of the plaque is described by some but not emphasized, for the healthy vessel wall has not been shown to have its own blood-carrying channels except in the adventitia and outer half of the media, and no implication of such channels playing any significant rôle in the manifestation of atherosclerosis

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has been forthcoming. They have been stressed in syphilis and also in rheumatic fever, but these have been regarded as specific types of lesions and not pertinent in any consideration of atherosclerosis.

The methods adopted for this study involve the clearing of tissues by well-known means to increase their translucency. The principles involved require no elaboration; the optical nature of the clearing agent as well as its solvent or other action on the tissues plays a rôle in the effectiveness of the whole process. In addition, the removal of mineral deposits by decalcification either prior to clearing or after, with re-clearing in the latter event, is an invaluable aid, bringing to view hitherto undisclosed channels which are then available for gross or micro-injection with the aid of the dissecting microscope. The latter is an indispensable equipment, allowing the clearing processes to be followed closely, and facilitating dissection of the various coats of an artery.

It has been possible to demonstrate a remarkably extensive pattern of circulation in the aorta of the cow. When the vessel is injected with India ink from the proximal end, with the branches and distal end ligated, the adventitial circulation becomes evident at once. These vessels in the cleared specimen are seen to penetrate the media for a great distance and at times actually to connect with the lumen of the vessel through very small orifices. When the aorta is opened and a wide-mouthed cannula connected with an injection apparatus is placed over the mouth of a branch, small vessels arising from the lip of the mouth of the branch become conspicuous. These course under the intima and anastomose freely with the above described adventitial vessels and with the branches of the minute vessels which arise independently from the lumen of the aorta. When the injection cannula is placed over such a minute orifice, this vessel may be injected independently. The rami of vessels arising from these several sources: (1) the adventitia, (2) the mouths of branches, (3) independent orifices, anastomose freely in the wall of the aorta of the cow. This pattern is demonstrable to a variable extent in the vessels of several species of animals.

The developmental basis for such a vascular pattern has been laid by the careful investigations of Bremer.[1] The pattern is demonstrated with facility in the veins of man, and it is unnecessary to do more than direct attention to the heart—an adapted vessel with its coronary and so-called thebesian circulation as described recently by Wearn and his associates[2]—to realize that it would not be remarkable if a similar pattern were demonstrable in the arterial wall of man. That this pattern is difficult to show in its entirety in all human arteries is undeniable. Frequently, however, in the coronaries and in the abdominal aorta very minute vessels are encountered arising independently from the wall and running to the adventitia where they anastomose in the rich adventitial

plexus. Occasionally such vessels, as they penetrate the aorta, are seen to give off small branches to the intima and media. After examination of many human arteries, it must be emphasized that vessels are seldom demonstrable in the intima or in the inner half of the media when no irritative, obliterative, or morbid process is present. The basic pattern becomes clearly visible, however, and often exaggerated in many of the processes that involve the vessel, including, in addition to atherosclerosis, the physiological obliterations as in the ductus arteriosus, and the lengthening and inelasticity associated with senility. Emphasis is laid upon this vascular pattern since in its topographical extent it partially determines the location and nature of the pathological processes.

One of the commoner manifestations of this vascularity is hemorrhage in the wall of blood vessels, occurring in or between any of the several coats, and sharing with the vascular network the safety of relative obscurity until injection and clearing bring both to view. The extent and status of the extravasated blood vary. It occurs as scattered well-preserved free cells, as phagocytized particles in the monocyte and as a residue of iron, demonstrable with Turnbull's well-known Prussian blue reaction. It is found in the grossly opaque yellow linear patches encountered in the aorta, often in young people dying of acute disease. It is found again as larger bright red, more or less oval masses in the depths of a thickened intima where supposedly there are no vessels. Again the extravasation may be more diffuse, like an ecchymosis. There is every reason to believe that such escaped blood can assume the characteristic forms of hemorrhage in any other tissue, modified only by the physical characteristics of the area in which it finds itself.

Such hemorrhages are encountered with great frequency and are not confined to any vessel or group of vessels. The literature cites instances of adventitial hemorrhages occurring both in man and in animals subject to a number of different diseased states, but as far as is known they are not frequently described in the intima or the media. In a recent publication Paterson,[3] in studying a series of coronary arteries in which thrombosis had occurred, discusses hemorrhage in the intimal tissue and describes small vessels in the intima arising from the lumen.

It is not surprising that many hemorrhages are seen at or near the origin of branches, since the small vasa which so frequently arise from the lips of such branches divide and subdivide to form an extensive plexus about the branch and also extend for some distance in the wall of the artery. These small vessels are seen frequently to be compressed around an oval clot in the wall, to run to the edge of a clot, or to course through areas of extravasated blood. Likewise, small vessels are found which arise from the lumen directly and which can best be described as trees with the bases of their trunks at the surface of the intima, their ramifying branches ornamenting the depth of the intima and every now

and again coming into contact with a hemorrhage. The impression must not be given that vascularity and hemorrhage are always coincidental, for this is not the case. While it is usually possible to demonstrate vascular channels in association with hemorrhage, this is not invariably true, and certainly very extensive vascular channels, even sinusoid-like passages, are found in the thickened intima where no hemorrhage can be seen.

Subsequent changes of the extravasated blood in the intima again reveal unexpected findings. There appears to be a gradual accumulation at the site of the hemorrhage of fatty material which is stainable with sudan III and which frequently contains the so-called "cholesterin clefts," giving the appearance of the classical atheroma. It is reasonable to suppose, therefore, that this fatty material is derived from, and eventually replaces, the blood of the original hemorrhage, a process analogous to the apparent changes observed in hemorrhages in thyroid adenomas and in cavernous hemangiomas. Such a conclusion is borne out by the fact, repeatedly confirmed, that a typical yellow atheromatous plaque may, on careful examination by the methods outlined above, show at its periphery a network of capillaries containing red blood cells and anastomosing, outside the zone of fat and necrosis, with obviously well-delineated and well-functioning blood channels. Often, too, the injection mass will merge with the blood and the cholesterin-containing fatty material of the atheroma. This happens only when the atheroma has softened, as it undoubtedly does at some stage. Evidence to support the statement is encountered when a partially disintegrated, bulging mass that resembles an egg yolk in color is cut with a sharp razor and its viscid content escapes. Naturally when such a focus in the intima extends to and through the endothelial lining of the lumen, it may discharge itself to form an atheromatous ulcer, and in such a cavity fresh blood may accumulate not only from the lumen but also from bleeding vessels in the depths of the crater.

The transformation of the fat-rich necrotic mass into calcified material may take place by a mechanism similar to that described by Klotz, involving saponification of fatty acids to form calcium soaps with subsequent transformation into calcium phosphate and carbonate. On such a basis the form of the ultimate concretion, whether sheetlike or roughly spherical, would depend upon the shape of the original extravasation or perhaps upon another fact, quite the same in principle though dependent upon slightly different physical conditions, which will be described in the following paragraph.

As has been said, the vascular channels may become very conspicuous in the thickened intima. Often they tend to arrange themselves parallel to the lumen of the vessel, and they may be traced from their origin at the intima above the thickening to their exit from the wall below the

thickening, perhaps into the lumen of the same mother vessel or into the large channel of a nearby branch. The impression is obtained that they may act as by-passes or detours when the lumen of the mother vessel is narrowed and even obliterated. The similarity of this intramural pattern to that of extramural adventitial collaterals, so strikingly depicted by Luigi Porta[4] as long ago as 1845 after experimental ligation of arteries, sustains this interpretation. The pattern may become very intricate, and the differentiation between it and the complex canalization of thrombi may become very difficult, if not impossible. This phase will not be dealt with now. Attention is drawn to these intramural channels, which are often larger than the narrowed lumen of the original vessel, because they are subject to great variations in length and width, and despite the free anastomoses that they frequently exhibit may be isolated from the circulation by constriction of their mouths by one or another event. If this happens, the blood in these vessels stagnates, and it is probable that clotting may occur, although evidence for this has not been developed. Blood in such a vessel may go through all the transformations of an extravasation within the vessel wall, as described above. And it may be converted through the fatty stage to stone. This, then is the formation of a "lith" from blood—a second method for the production of calcified masses.

Among the interesting facts encountered none have been more illuminating than those associated with obliteration of the ductus arteriosus. At birth its wall seems quite avascular; within twelve hours, when it may be contracted to partial occlusion, vessels are demonstrable in the wall arising either from the adventitia or the intima. At two months the lumen is more or less occluded by an extremely vascular connective tissue, the vessels of which come from the intima of the pulmonary artery and aorta, as well as from the adventitia of the ductus. They vary in width, and sinusoid-like dilatations are not infrequent. Even at this age opacities and concretions are found in these dilated channels, and in specimens from older individuals more or less calcification is encountered. The entire ductus may be a series of such stones, and they may extend to the subintima of the aorta where a sheet of hard lime may be spread out and may surround the closed orifice of the ductus.

Obviously, the blood encountered so frequently in the walls of the blood vessels can only get there through preexisting channels. "Skimmers" that function to accumulate fluid without formed blood elements have not been demonstrated. The question concerning the nature of the tissue response to the extravasated blood cannot be more than touched upon at this time. The proliferated intimal tissue varies tremendously in the proportion of capillary vessels and connective tissue, as has been frequently demonstrated by both injection and by study of stained sections. This variability may be dependent upon the presence of specific stimuli, as well as upon intrinsic constitutional factors.

SUMMARY

The above presentation attempts to emphasize the following:

1. The importance of continuity of anatomical study so that topographical relations are clarified rather than lost by higher magnifications.

2. The value of clearing agents and of injection masses in such study.

3. The pattern of mural circulation in the vascular system including the arteries and the veins in man and beasts.

4. Hemorrhage derived from intramural circulation as an important element in the development of atherosclerosis.

REFERENCES

1. Bremer, J. L.: The Origin of the Renal Artery in Mammals and Its Anomalies, Am. J. Anat. **18:** 179, 1915.
2. Wearn, J. T., Mettier, S. R., Klumpp, T. G., and Zschiesche, L. J.: The Nature of the Vascular Communications Between the Coronary Arteries and the Chambers of the Heart, AM. HEART J. **9:** 143, 1933.
3. Paterson, J. C.: Vascularization and Hemorrhage of the Intima of Arteriosclerotic Coronary Arteries, Arch. Path. **22:** 313, 1936.
4. Porta, Luigi: Delle alterazioni patologiche delle arterie per la legatura e la torsione, Milan, 1845.

HYPERTENSION PRODUCED BY CONSTRICTION OF THE RENAL ARTERY IN SYMPATHECTOMIZED DOGS*

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HYPERTENSION has been consistently produced in experimental animals by compression of the renal artery.[1-4] No entirely satisfactory explanation for the rise in blood pressure has yet been offered. Evidence has been presented that the hypertension occurs in spite of removal of one adrenal and denervation or demedullation of the other.[1] Bilateral splanchnic nerve resection does not alter it[5] nor does section of the anterior spinal nerve roots from sixth thoracic to the second lumbar segments.[21] The renal nerves are not necessary for its development.[2, 3] Since the control of the arterial pressure is chiefly dependent upon the peripheral resistance, the cardiac output and the blood volume, the part played by these physiological mechanisms in the genesis of experimental hypertension was investigated.

METHODS

Dogs were used in all of our experiments. They ranged in weight from 9 to 15 kilos. The systolic and diastolic blood pressures were taken by the auscultatory method.[3, 6, 7] The bell of the stethoscope measured 2.2 cm. in diameter and was strapped to the anterior medial aspect of the ankle, at or just above the joint. A pneumatic cuff 5 cm. in width and 14 cm. long, encased in a cloth bag 5 by 28 cm. was wound around the leg just above the ankle. The dog was trained to lie on its right side and the pressure taken from the right hind leg. Systolic blood pressure values obtained by the auscultatory method agreed closely with those obtained in two dogs with van Leersum carotid loops.

Hypertension was produced by constriction of the renal arteries, as first described by Goldblatt, Lynch, Hanzal, and Summerville.[1]

Total sympathectomy was performed in three or four stages under amytal (25 mg. per kg.) and intratracheal, positive-pressure, ether anesthesia. The technique employed was similar to that described for cats by Cannon, Newton, Bright, Menkin, and Moore.[8] Care was taken to ensure complete removal of the sympathetic chains. At the first stage of the operation, the right thoracic sympathetic chain was removed from the stellate to the twelfth thoracic ganglion. A black thread or silver clip was attached to the upper end of the right abdominal chain as a

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marker. At the second stage, through an abdominal incision, the right chain was freed from the promontory of the sacrum and was followed up under the diaphragm until the marker was reached. At the same stage, the left abdominal chain was resected from the fifth lumbar ganglion to the diaphragm and a marker was placed on the lower end of the left thoracic chain. At the final stage, the left thoracic chain was followed down from the stellate to the twelfth thoracic ganglion, under the diaphragm, until the marker was located.

Cardiac denervation and thoracic sympathectomy were performed in two stages by the intrathoracic approach. A modification of the technique used in cats, described by Cannon, Lewis, and Britton[9] was employed. Through the fourth right interspace the sympathetic chain was freed from the eighth thoracic ganglion to the stellate ganglion. After the branches of this ganglion to the brachial plexus and intercostal nerves had been severed, the parietal pleura just cephalad to the innominate vein was incised. By blunt dissection the vagus nerve was exposed and the recurrent laryngeal nerve identified in its course around the subclavian artery. The middle cervical ganglion is intimately attached to the vagus approximately at the point at which the recurrent laryngeal nerve leaves the trunk.[10] All branches of the right recurrent nerve were severed and the vagus trunk divided below the point at which the recurrent laryngeal leaves it. The trunk was then again divided below the middle cervical ganglion and after division of one arm of the ansa Vieusseni, the sympathetic chain was removed with the middle cervical ganglion and a segment of the vagus trunk in one piece.

On the left side, an incision was made in the fourth interspace. The stellate ganglion was identified and all the branches divided except one limb of the ansa Vieusseni. This limb was then followed up to the middle cervical ganglion. By sharp and blunt dissection this ganglion was freed from the vagus and was removed with the sympathetic chain to the eighth thoracic ganglion. All branches of the left vagus were cut from the region just above the site of the middle cervical ganglion to the root of the lung. By this operation, all cardiac nerves were severed, while the recurrent laryngeal nerve was saved on the right side. On the left side the main trunk of the vagus was saved to supply the gastrointestinal tract.

The plasma volume was measured by spectrophotometric determination of the disappearance curve of the dye "T-1824" according to the technique of Gregersen, Gibson, and Stead.*[11]

RESULTS

A. *Sympathetic Vasomotor Control.*—Total sympathectomy did not prevent the development of hypertension from compression of the renal arteries. The result presented in Fig. 1 was confirmed in six other dogs.

*The dye was obtained through the kindness of Dr. Gregersen.

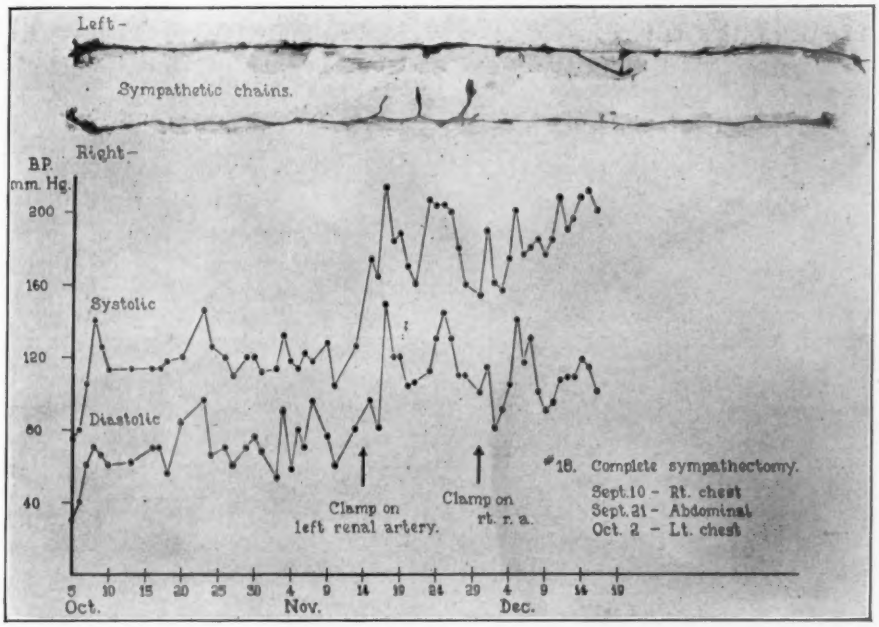

Fig. 1.—Effect of application of Goldblatt clamps to renal arteries on systolic and diastolic blood pressure of sympathectomized dog. The unbroken sympathetic chains are shown above the chart.

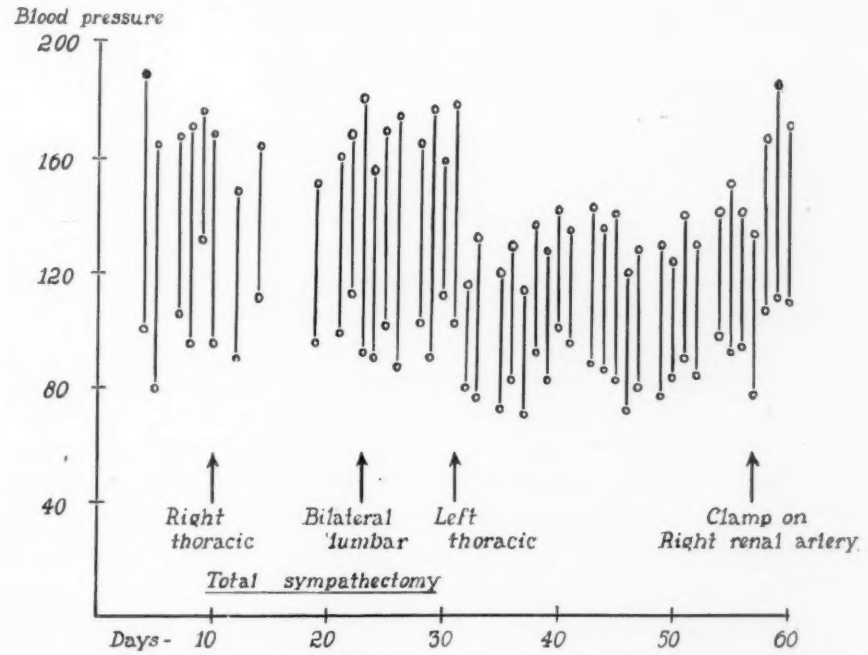

Fig. 2.—Reduction of spontaneous high blood pressure in dog by total sympathectomy. Hypertension then produced by constriction of the right renal artery.

Fig. 2 illustrates the decrease which was produced by sympathectomy in a dog with spontaneous elevation of blood pressure. With the pressure at a normal level following sympathectomy, application of a Goldblatt clamp to the right renal artery caused a prompt increase of the pressure to a hypertensive level.

In contrast to the reduction of blood pressure produced by sympathectomy in the normal dog, with moderate spontaneous elevation of blood pressure, Fig. 3 shows that the hypertension produced by compression of the renal arteries was not materially affected by sympathectomy.

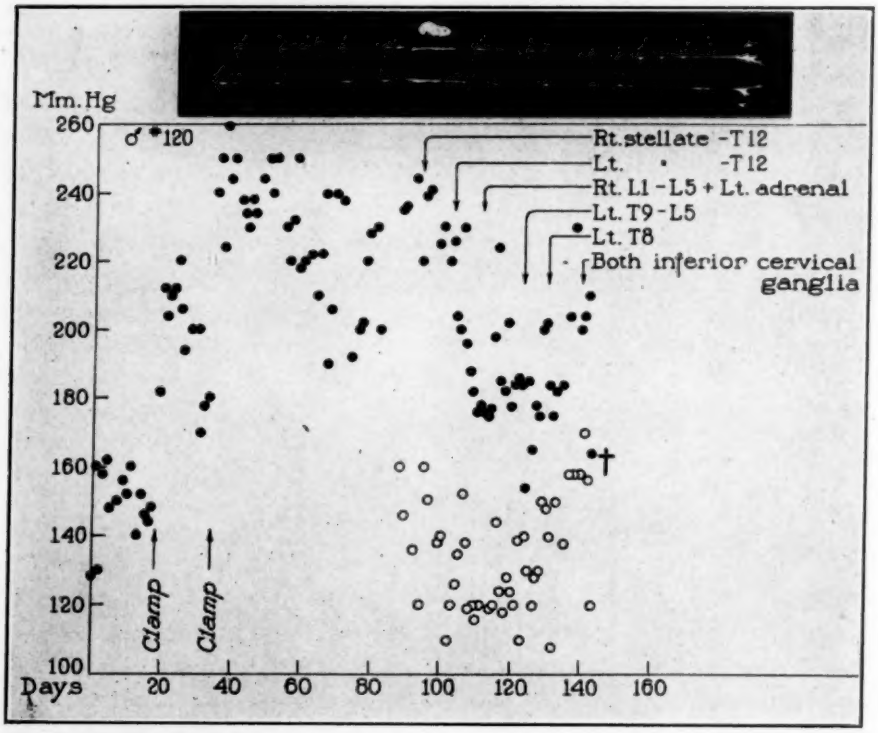

Fig. 3.—Showing that the hypertension produced by compression of the renal arteries is not materially affected by progressive sympathectomy. A photograph of the two sympathetic chains and the adrenal gland is shown at the top of the chart.

If the elevated blood pressure in the dog made hypertensive by constriction of the renal arteries was the result of increased sympathetic activity, a fall in blood pressure would be expected upon the administration of large doses of ergotamine tartrate.[12] On the contrary, in two dogs, an additional rise was obtained as depicted in Table I. These data are merely suggestive as it was not possible to reverse the pressor effect of 0.3 c.c. of 1:1000 adrenalin (intravenous) by such large doses as 3 mg. of ergotamine tartrate given by vein in unanesthetized hypertensive dogs.

TABLE I

EFFECT OF INTRAVENOUS ADMINISTRATION OF ERGOTAMINE TARTRATE ON BLOOD PRESSURE OF DOG WITH HYPERTENSION FROM COMPRESSION OF THE RENAL ARTERIES

Control B.P. level = 210 mm. Hg	
1 mg. gynergen intravenously	
4 minutes	later B.P. = 206-216 mm.
8 minutes	later B.P. = 230
10 minutes	later B.P. = 240
20 minutes	later B.P. = 216
24 hours	later B.P. = 190-200. Heart rate 86.
3 mg. gynergen intravenously	
10 minutes	later B.P. = 240-250. Heart rate 48.
25 minutes	later B.P. = 230. Vomited.

B. *Reflex Cardiac Control.*—Total sympathectomy in the dog does not abolish the power of reflex cardiac acceleration, since cardio-accelerator fibers have been reported to run in the vagus nerves.[13] It was therefore possible that the rise in blood pressure in the sympathectomized dog, after application of clamps to the renal arteries, was due to the reflex cardiac excitation. Fig. 4 shows the rise in heart rate with elevation of blood pressure from the administration of atropine sulfate (0.2 mg. per kilo, intravenously) to the completely sympathectomized dog.

After the heart has been denervated by intrathoracic section of all the cardiac nerves, no acceleration takes place after the administration of atropine. In Fig. 5 are presented parts of the original record taken from one of the four dogs in which cardiac denervation was successfully completed. In none of these animals was hypertension from compression of the renal arteries prevented.

Combined total sympathectomy and cardiac denervation was successfully performed on one hypertensive dog. Even in this animal, as can be seen in Fig. 6, the hypertension was not reduced. A clamp was applied to the left renal artery at the last stage of the total sympathectomy. A slight additional rise in blood pressure was observed after this operation.

After the first two operations, the heart was completely denervated. Acceleration is then chiefly dependent upon the secretion of adrenine. At the third stage, the right adrenal was denervated by removal of the remainder of the right sympathetic chain. The left adrenal was still normally innervated. It may be seen from the chart (Fig. 6), that the basal heart rate over the week preceding the final stage varied between 92 and 104 beats per minute. After the fourth operation, when the remaining adrenal was denervated by removal of the remainder of the left sympathetic chain, the rate of the denervated heart did not decrease.

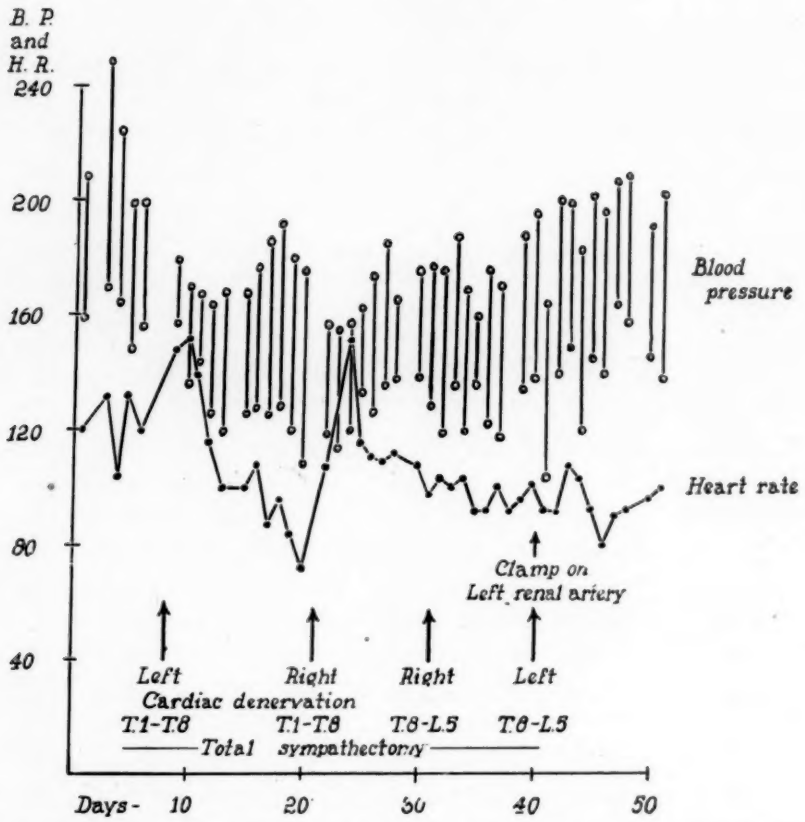

Fig. 4.—Effect of atropine sulfate on heart rate and blood pressure of sympathectomized dog.

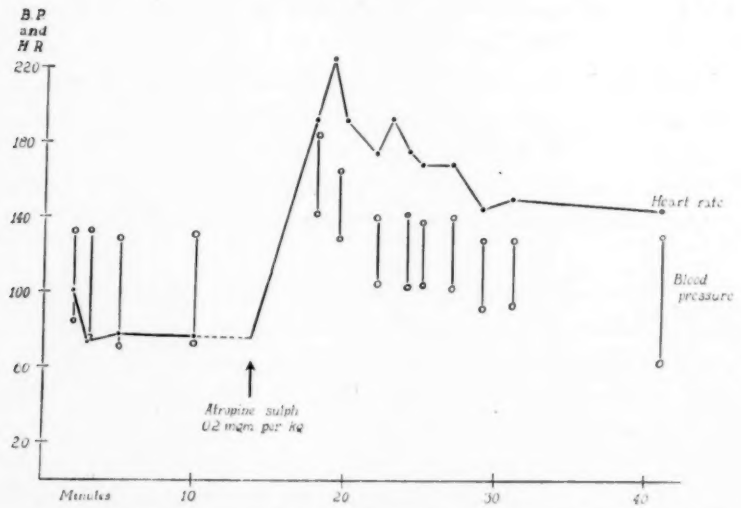

Fig. 5.—Effect of atropine sulfate on heart rate of sympathectomized dog with denervated heart.

This stability of heart rate, indicated that there probably was not an increased medulliadrenal secretion during the course of hypertension produced by compression of the renal artery.

C. *Blood Volume.*—The third physiological mechanism to be investigated as a possible source of elevation of blood pressure, was the plasma

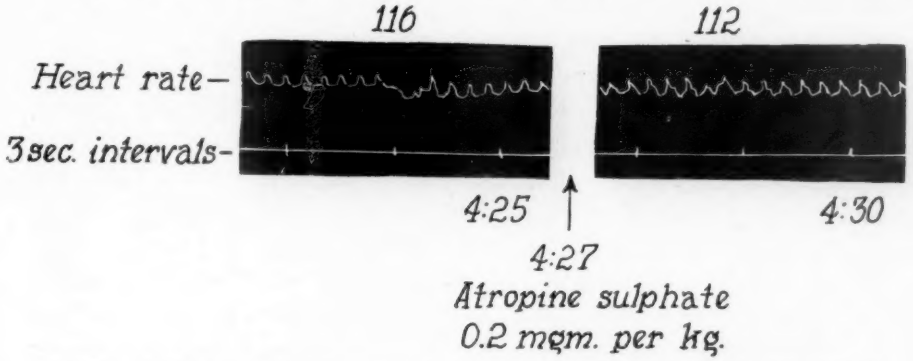

Fig. 6.—Effect of cardiac denervation and total sympathectomy on heart rate of dog with hypertension produced by compression of renal arteries. Right renal artery clamped two weeks before experiment started.

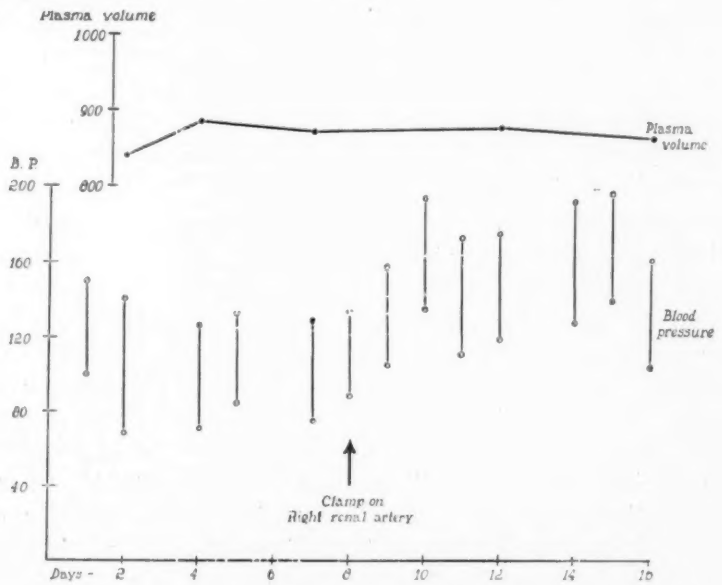

Fig. 7.—Effect of hypertension produced by constriction of renal artery on blood pressure and plasma volume of sympathectomized dog.

volume. It was determined on one normal and two sympathectomized dogs before and after the production of hypertension. As can be seen from Fig. 7, there was no demonstrable increase in the plasma volume as the dog developed hypertension. This result was confirmed in the normal and second sympathectomized dog.

COMMENT

The production of hypertension by compression of the renal arteries in the completely sympathectomized dog (Figs. 1, 2, 6 and 7) is in accord with the observations of other investigators[1, 2, 3, 5, 21] who studied the effects of partial sympathectomy on this type of hypertension. The completeness of the operative procedures in these experiments was confirmed by inspection of the sympathetic chains (Figs. 1 and 3). Postmortem dissection of three sympathectomized dogs, which died several days after the production of hypertension, failed to disclose overlooked ganglia or regenerated sympathetic fibers.

Resection of both thoracolumbar chains, although it disconnects the blood vessels from reflex control of the sympathetic nervous system, does not remove all the sympathetic ganglia. There are ganglia located in the periphery, such as the superior cervical, celiac, superior and inferior mesenteric ganglia, which may be of significance. Evidence has recently been brought forward by Govaerts,[14] that a discharge of impulses takes place from the stellate ganglion, even though the preganglionic sympathetic fibers coming to it from the spinal cord have been divided. These observations have not yet been confirmed. Even though these outlying sympathetic ganglia are found to be physiologically active, it is unlikely that they are of significance in the development or maintenance of hypertension since their connections with the central nervous system have been severed. There is still the possibility, however, that they might be activated through stimulating agents carried by the blood stream.

The blood pressure of normal dogs drops for some days after removal of both sympathetic chains.[7, 15] In one of our animals with spontaneous hypertension (Fig. 2) a similar fall is illustrated. The hypertension produced by denervation of the carotid sinuses and section of the depressor nerves, also disappears after total sympathectomy.[16] Yet in the dogs in which hypertension was produced by compression of the renal arteries, the blood pressure was not reduced to normal, even immediately after operation (see Figs. 3 and 6). In "carotid sinus" hypertension, an increase in adrenal secretion has been noted.[17] In our experiments, there was no evidence of an increase in activity of the adrenal medulla (Fig. 6). From these observations, it would seem unlikely that the hypertension from compression of the renal arteries was the result of increased activity of the sympathetic nervous system or the adrenal medulla.

The completely sympathectomized dog is able to engage in vigorous physical work with only slight impairment of efficiency.[18] The increased cardiac activity produced through the cardio-accelerator fibers of the vagus nerves, probably assists in maintaining an adequate head of pressure in the arterial system. In order to eliminate reflex cardiac

control as a mechanism for the production of "renal" hypertension, it was necessary to denervate the heart by intrathoracic section of all cardiac nerves. Even denervation of the heart, combined with total sympathectomy (Fig. 6), did not prevent the development of hypertension.

Determinations of the plasma volume in experimental "renal" hypertension have not been reported. In clinical cases of nephritis[19] and hypertension[20] no consistent increase has been observed. The unchanged plasma volume in hypertensive dogs, found in these experiments, is in agreement with the observations in clinical cases.

SUMMARY

1. Complete sympathectomy, in seven dogs, did not prevent the development of hypertension from compression of the renal arteries.

2. The level of the hypertension was not materially affected during the course of total sympathectomy.

3. There was no evidence of increased medulliadrenal secretion.

4. Injection of ergotamine tartrate (3 mg.) produced a slight further increase in the hypertension in two dogs but this dose was insufficient to reverse the pressor effect of adrenalin (0.3 c.c. 1:1000 intravenously).

5. Denervation of the heart, combined with total sympathectomy, did not influence the course of the hypertension.

6. The plasma volume, in one normal and in two sympathectomized dogs, was not increased as the hypertension developed.

CONCLUSIONS

Hypertension produced by compression of the renal arteries is not mediated through increased peripheral resistance of reflex sympathetic vasomotor origin.

It is not the result of reflex changes in cardiac activity.

It is not accounted for by an increased volume of plasma.

These observations suggest that the known physiological factors which normally control the level of arterial pressure are not etiologically significant in the genesis of experimental hypertension, produced by compression of the renal arteries.

REFERENCES

1. Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension. I. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, J. Exper. Med. **59**: 347, 1934.
2. Page, I. H.: The Relationship of the Extrinsic Renal Nerves to the Origin of Experimental Hypertension, Am. J. Physiol. **112**: 166, 1935.
3. Collins, D. A.: Hypertension From Constriction of the Arteries of Denervated Kidneys, Am. J. Physiol. **116**: 616, 1936.
4. Wood, J. E., Jr., and Cash, J. R.: Experimental Hypertension—Observations on Sustained Elevation of Systolic and Diastolic Blood Pressure in Dogs, J. Clin. Investigation **15**: 543, 1936.

5. Goldblatt, H., Gross, J., and Hanzal, R. F.: Studies on Experimental Hypertension. II. The Effect of Resection of Splanchnic Nerves on Experimental Renal Hypertension, J. Exper. Med. **65**: 233, 1937.
6. Allen, F. M.: Auscultatory Estimation of the Blood Pressure of Dogs, J. Metabolic Research **4**: 431, 1923.
7. Cannon, B.: The Effects of Progressive Sympathectomy on Blood Pressure, Am. J. Physiol. **97**: 592, 1931.
8. Cannon, W. B., Newton, H. F., Bright, E. M., Menkin, V., and Moore, R. M.: Some Aspects of the Physiology of Animals Surviving Complete Exclusion of Sympathetic Nerve Impulses, Am. J. Physiol. **89**: 84, 1929.
9. Cannon, W. B., Lewis, J. T., and Britton, S. W.: Studies on the Conditions of Activity in Endocrine Glands. XVII. A Lasting Preparation of the Denervated Heart for Detecting Internal Secretion, With Evidence for Accessory Acclerator Fibers From the Thoracic Sympathetic Chain, Am. J. Physiol. **77**: 326, 1926.
10. White, J. C., Garrey, W. E., and Atkins, J. A.: Cardiac Innervation, Arch. Surg. **26**: 765, 1933.
11. Gregersen, M. I., Gibson, J. J., and Stead, E. A.: Plasma Volume Determination With Dyes: Errors in Colorimetry; Use of the Blue Dye T-1824, Am. J. Physiol. (Proc.) **113**: 54, 1935.
12. Dale, H. H.: On Some Physiological Actions of Ergot, J. Physiol. **34**: 163, 1906.
13. Jourdan, F., and Nowak, S. J. G.: Les Fibres Cardio-accélératrices dans le Nerf Pneumogastrique du Chien, Compt. rend. Soc. de biol. **117**: 234, 1934.
14. Govaerts, J.: Contribution à l'étude de l'innervation sympathique du coeur, Arch. internat. de méd. expér. **11**: 630, 1936.
15. Wilson, H., Roome, N. W., and Grimson, K.: Complete Sympathectomy. Observations of Certain Vascular Reactions During and After Complete Exclusion of the Sympathetic Nervous System in Dogs, Ann. Surg. **103**: 498, 1936.
16. Heymans, C., and Bouchaert, J. J.: Hypertension Artérielle Experimentale et Sympathectomie, Compt. rend. Soc. de biol. **120**: 82, 1935.
17. Heymans, C.: Le Sinus Carotidien, G. Doin et Cie, Paris, 106, 1933.
18. Brouha, L., Cannon, W. B., and Dill, D. B.: The Heart Rate of the Sympathectomized Dog in Rest and Exercise, J. Physiol. **87**: 345, 1936.
19. Linder, G. C., Lundsgaard, C., Van Slyke, D. D., and Stillman, E.: Changes in the Volume of Plasma and Absolute Amount of Plasma Proteins in Nephritis, J. Exper. Med. **39**: 921, 1924.
20. Schmidt, W., Blutmengen-Besttimmungen bei Nieren und Herzkrankheiten, Ztschr. f. d. ges. exper. Med. **58**: 276, 1927.
21. Page, I. H.: Unpublished observation.

THE PHYSIOLOGICAL EFFECTS OF EXTENSIVE SYMPATHECTOMY FOR ESSENTIAL HYPERTENSION*

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THIS study of physiological changes resulting from extensive sympathectomy is based on forty-five patients who were operated on for essential hypertension from February, 1935 to January, 1937. Studies of patients operated on since January, 1937 are not included in this report. The technique used, which has been described in detail elsewhere,[1, 3] consists of bilateral subdiaphragmatic, extraperitoneal resection of the splanchnic nerves, celiac ganglions, and the upper two lumbar sympathetic ganglions. The second operation is performed about ten days after that on the opposite side. In twenty-five instances partial suprarenalectomy was performed; one-third to two-fifths of each gland was removed to see if this would accentuate the effects on blood pressure of extensive sympathectomy. Surgical treatment of hypertension has been attempted because it is apparent that there is no means of controlling hypertension adequately, by nonsurgical management, in many instances; the high mortality from hypertension is adequate testimony for this observation.[1, 2]

It is known that elevation of blood pressure in essential hypertension is due to a generalized increase in resistance to the flow of blood through the periphery of the arterial system. The fault, which seems to be that of the arterioles chiefly, appears to be abnormal vasoconstriction or increased arteriolar tonus, at least in early stages of hypertension. Later in the disease organic changes affecting small arteries and arterioles may contribute to increased resistance to the flow of blood through them. There is evidence that, at least in early hypertension, the abnormal state of the arterioles is an expression of abnormal vasomotor stimuli arising in the vasomotor center, which are transmitted to arterioles by way of sympathetic nerves, or that the arterioles respond with an abnormal state of vasoconstriction or tonus to normal stimuli transmitted by way of the sympathetic nervous system. In advanced hypertension the arterioles may assume an independent function of increased resistance to the flow of blood through them either by virtue of structural changes or by virtue of an inherently increased tonus independent of stimuli transmitted over the sympathetic nervous system from the vasomotor center. Goldblatt's experimental work[7] has shown that diminution of blood supply to the kidneys produces hypertension closely simulating essential hy-

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pertension of man. Whether or not this mechanism of elevation of blood pressure is effective in essential hypertension of man cannot, at present, be either categorically affirmed or denied but the possibility of it must be considered.

The chief purposes of sympathectomy are disconnection of the arterioles from the vasomotor center, thus inducing a state of decreased tonus or of decreased vasoconstriction, and of increasing blood flow through the kidneys by performing sympathetic denervation of them. The reduction of blood pressure by operation may depend on either or both of these effects which may decrease the resistance offered by arterioles to flow of blood through them. Previous experience with cervicothoracic and lumbar sympathectomy indicated that these procedures were of little avail in the treatment of essential hypertension. The failure of these procedures seemed based largely on the probable fact that too small a part of the arteriolar bed was sympathectomized or that sympathetic denervation of the kidneys was not accomplished. The next logical step was splanchnic and upper lumbar sympathectomy, for within the abdomen there exists a relatively enormous arteriolar bed. Diminished liberation of epinephrine from the suprarenal glands may occur incidental to operation and may perhaps contribute importantly to reduction of blood pressure. Also extensive sympathectomy for hypertension may decrease a state of increased tonus in the arterioles of the kidneys, thus improving circulation to them and reducing blood pressure.

Experience has taught us that the surgical procedure employed does not produce uniform effects on blood pressure. We recognize that return of the blood pressure to normal is desirable in essential hypertension but that this does not occur routinely as a result of operation. However, we believe that while such an accomplishment is desirable it is not necessary, for substantial reduction of the blood pressure may relieve symptoms, prevent the disastrous results of sustained abnormally high blood pressure, and prevent marked increases in blood pressure resulting from emotional stimuli which are themselves harmful. We do not believe that surgical operation for hypertension is necessarily the ultimate contribution to the treatment of this serious condition but the results which we have observed following operation have encouraged us to continue with this type of treatment until a better method has been devised.

SELECTION OF PATIENTS WITH ESSENTIAL HYPERTENSION FOR EXTENSIVE SYMPATHECTOMY

Some patients with essential hypertension do not require operation for the elevation of blood pressure is not great, does not gradually increase, and does not produce significant changes in the arterial system. Perhaps, as more information is gathered relative to the effects of operation, more patients who have mild, apparently nonprogressive

hypertension will be operated on as a prophylactic measure. However at present we reserve operation, largely, for patients whose hypertension, if mild, is definitely progressive in spite of medical supervision and for those who have severe hypertension which has not responded to medical treatment. Following extensive sympathectomy the blood pressure is not decreased in the same degree in all cases of essential hypertension in which permanent reduction of blood pressure is an urgent need. If patients of this classification who have this disease are operated on, the results vary from extremely good to very poor. This has led us to attempt to select, from a large group of patients who have essential hypertension, those whose blood pressures will respond favorably to operation. We know no infallible criteria for such a selection at the present time. However, patients whose blood pressures decrease to normal or nearly to normal as results of rest or sleep, of oral administration of 3 grains (0.2 gm.) of sodium amytal hourly for three successive hours, of administration of one-half grain of sodium nitrite at half-hour intervals for three hours, and of the slow, intermittent, intravenous injection of a 5 per cent solution of pentothal sodium for light anesthetization, receive the greatest benefit from operation.[4*] Good results from these tests indicate to us that the arterioles offer increased resistance to flow of blood through them largely by virtue of functional, hence reversible changes; not as a result of organic, hence largely irreversible changes. Conversely, those patients whose blood pressures do not decrease satisfactorily as a result of these measures, benefit from operation, as a group, to a substantially less degree than do those whose pressures are still labile.

Unfortunately for extreme accuracy of prediction of results of operation, an occasional but infrequent patient whose blood pressure does not decrease satisfactorily as a result of rest, of administration of amytal, of sodium nitrite, or of pentothal, receives benefit from operation while not infrequently a patient for whom prediction of excellent operative effects on blood pressure, based on satisfactory responses to the tests mentioned before operation, receives much less than the expected benefit from operation. In Table I it is shown that when the response of the blood pressure to intravenous injection of pentothal is unfavorable the results of operation are almost uniformly unfavorable and that when the response of the blood pressure to the intravenous injection of pentothal sodium is fairly good, the eventual result is fairly good. However, when the responses of the blood pressure to the intravenous injection of pentothal sodium are good, the eventual effects of operation on the blood pressure are occasionally much less satisfactory. Since the greatest errors in predicting results occur when good results of operation are anticipated and since the tendency is to predict too good results on the basis of preoperative tests, we believe

*Incomplete studies indicate that pressure on carotid sinuses may affect blood pressure to much the same degree that rest, amytal, sodium nitrite, and pentothal affect it.

TABLE I

EFFECTS ON BLOOD PRESSURE OF PENTOTHAL AND EXTENSIVE SYMPATHECTOMY

RESPONSE OF BLOOD PRESSURE		RESULT OF OPERATION		ACCURACY OF PREDICTION
TO PENTOTHAL	TO OPERATION*	PREDICTION	ACTUAL	
158/132	Dead in seven mo.	Poor	Poor	Good
170/130	160/120 (9)†	Poor	Poor	Good
165/122	155/110 (11)	Poor	Poor	Good
184/134	255/160 (9)	Poor	Poor	Good
146/106	168/100 (9)	Fair	Fair	Good
150/112	154/106 (8)	Fair	Fair	Good
158/112	190/120 (7)	Fair	Poor	Poor
154/110	194/120 (9)	Fair	Poor	Poor
148/114	200/130 (6)	Fair	Poor	Poor
154/116	170/115 (2)	Fair	Fair	Good
132/106	174/118 (10)	Fair	Fair	Poor
158/ 98	194/120 (6)	Fair	Poor	Poor
120/ 90	140/100 (5)	Good	Good	Good
142/100	150/ 90 (4)	Good	Good	Good
118/ 90	170/100 (10)	Good	Fair	Fair
140/100	180/110 (5)	Good	Fair	Fair

*Mean of three determinations.
†Months after operation.

it advisable to accept the least favorable response of the blood pressure to rest and sleep, and to administration of amytal, sodium nitrite, and pentothal as the basis of preoperative prediction. We do not consider apparent sclerosis of the retinal arteries, moderate enlargement of the heart, inversion of T-waves in electrocardiograms, albuminuria, slight reduction in renal function or cerebrovascular accident from which recovery has been satisfactory, contraindications, in themselves, to operation. However, we do not advise operation for patients who have congestive heart failure, marked renal insufficiency, advanced arteriosclerosis, or angina pectoris. Perhaps as experience increases some of these patients may be considered suitable subjects for operation.

MORTALITY AND MORBIDITY

A series of eighty-five successive operations has been performed without a death. Three patients have died subsequently. A girl, seven years of age, with hypertension of Group IV (malignant hypertension)[1, 2*] and repeated convulsions died seven months following operation which did not influence the blood pressure significantly. A man, aged forty-one years, with renal and myocardial failure owing to hypertension of Group II died seven months after operation which did not significantly influence blood pressure. A woman, twenty-five years old, with hypertension of Group III which was fixed sufficiently that the minimal blood pressures during rest and sleep were 160 and 120 died fourteen months following operation. Because of information we have gained we would consider none of these patients suitable candidates for operation at the present time. A patient whose blood pressure was very favorably influenced by operation and whose physical condition was good committed suicide because of depression resulting from business

*The classification of essential hypertension is that of Keith and Wagener.

worries. Two patients have had cerebral hemorrhages. The remainder of the entire group of patients are not disabled although the blood pressure of many of them was not greatly decreased by operation, as will be emphasized later. The symptoms of many patients of this group were not benefited by operation.

EFFECT OF OPERATION ON BLOOD PRESSURE AND PULSE RATE WHEN PATIENTS STAND

It is a common observation that after operation the blood pressure decreases and the pulse rate increases when the patient stands. While such reactions are common to some degree in many instances before operation, they are usually greatly exaggerated after operation (Table II). These disturbances undoubtedly account, at least in a major de-

TABLE II

EFFECT OF UPRIGHT POSTURE ON PULSE RATE AND BLOOD PRESSURE FOLLOWING OPERATION*

(TEN ILLUSTRATIVE CASES)

BLOOD PRESSURE				PULSE RATE			
BEFORE OPERATION		AFTER OPERATION		BEFORE OPERATION		AFTER OPERATION	
LYING	STANDING	LYING	STANDING	LYING	STANDING	LYING	STANDING
220/110	200/110	170/95	80/50	112	104	84	120
198/116	200/126	160/106	140/102	94	108	80	124
154/110	148/112	134/94	128/90	80	116	76	120
150/108	160/114	128/92	110/92	72	124	88	115
168/114	182/130	158/110	118/92	88	120	120	156
182/116	164/120	140/112	118/92	80	92	92	124
200/110	192/120	192/110	148/116	84	100	92	138
162/110	162/122	194/122	94/78	84	108	88	120
210/138	208/146	178/118	70/40			100	138
200/130	165/120	136/100	114/80			84	121

*Two to three weeks following operation.

gree, for weakness (and occasionally syncope), breathlessness, and palpitation which are commonly noted by patients when they stand following operation.

Usually orthostatic tachycardia and hypotension disappear gradually over variable periods following operation (Table III). This occurs independently of whether the effect of operation on the blood pressure was good, for in cases of poor and good results alike there is a gradual tendency of response of the pulse rate and blood pressure to the upright position to be less marked as time passes after operation. Frequently orthostatic tachycardia persists after orthostatic hypotension has disappeared.

EFFECT OF OPERATION ON THE RESPONSE OF THE BLOOD PRESSURE TO IMMERSION OF A HAND IN COLD WATER

We place a good deal of importance on the response of the blood pressure to a standard stimulus, for which we use the cold test devised by Hines and Brown.[8] This test is carried out by determining blood

TABLE III

THE EFFECT OF THE UPRIGHT POSTURE ON BLOOD PRESSURE; VARYING PERIODS AFTER OPERATION

(TEN ILLUSTRATIVE CASES)

TIME AFTER OPERATION	BLOOD PRESSURE	
	LYING	STANDING
Two weeks	170/120	160/115
Sixteen months	188/120	200/130
Two weeks	120/90	80/60
Four months	140/95	135/95
Two weeks	164/112	138/120
Ten months	214/130	234/140
Two weeks	194/122	94/78
Three months	230/135	255/160
Two weeks	168/112	132/100
Six months	160/140	152/130
Two weeks	170/95	80/50
Two months	210/126	192/120
Two weeks	148/104	134/110
Ten months	165/122	185/135
Two weeks	110/86	80/65
Ten months	108/88	134/98
Two weeks	134/96	122/90
Eight months	118/94	120/96
Two weeks	118/88	68/58
Four months	110/80	115/100

pressure with the patient resting, until it reaches a basal level. A hand is then immersed to the wrist in water at 4° C. for one minute and blood pressure determined at the end respectively of thirty seconds and of one minute of immersion of the hand. The highest value is considered characteristic of the response. We believe that the response of the blood pressure to this test is a measure of the way in which it responds on innumerable occasions to such stimuli as anxiety, fright, and mental stresses and strains. In Table IV it is shown that when the blood pressure has been favorably influenced by operation, the increase in it as a result of the cold test is greatly reduced in most instances. This is particularly true of the systolic blood pressure. When operation does not produce a significant decrease in the blood pressure, the response of it to the cold test is ordinarily less than before operation but distinctly abnormal (Table V). As in cases in which operation has produced significant decrease in blood pressure, the systolic blood pressure responds less sharply to the test than does the diastolic pressure.

EFFECT OF OPERATION ON SYMPTOMS RESULTING FROM HYPERTENSION

The effect of operation on symptoms, while variable, is roughly proportional to the effect on blood pressure. However, not infrequently patients note relief of headache, fatigue, pain in the chest, "dizziness," and nervousness in spite of the fact that the blood pressure has not

TABLE IV

RESPONSE OF THE BLOOD PRESSURE TO THE COLD TEST IN CASES IN WHICH THE EFFECT OF OPERATION ON THE BLOOD PRESSURE WAS FAVORABLE

(FIFTEEN ILLUSTRATIVE CASES)

BEFORE OPERATION	AFTER OPERATION
168/118 to 192/132	128/100 to 138/104
200/110 to 250/130	170/95 to 210/120
190/135 to 260/170	128/100 to 154/122
190/110 to 238/130	136/80 to 170/108
158/118 to 184/120	130/90 to 164/100
198/116 to 278/160	160/106 to 198/130
200/130 to 240/150	136/100 to 140/104
154/110 to 178/126	134/94 to 144/118
146/100 to 204/135	132/90 to 158/118
170/110 to 200/145	130/100 to 175/130
200/130 to 258/162	140/100 to 160/100
182/102 to 248/150	140/90 to 188/128
158/128 to 190/150	126/94 to 150/128
174/110 to 218/156	112/86 to 146/124
170/118 to 202/134	150/106 to 170/120

TABLE V

RESPONSE OF THE BLOOD PRESSURE TO THE COLD TEST IN CASES IN WHICH THE EFFECT OF OPERATION ON BLOOD PRESSURE WAS NOT FAVORABLE

(FIFTEEN ILLUSTRATIVE CASES)

BEFORE OPERATION	AFTER OPERATION
170/130 to 240/156	160/122 to 190/136
156/122 to 190/120	152/118 to 185/128
190/120 to 220/130	170/120 to 185/130
180/120 to 214/144	198/132 to 214/136
200/130 to 240/158	200/140 to 220/170
170/120 to 256/150	166/114 to 200/150
182/116 to 230/150	140/112 to 178/128
210/134 to 232/176	200/119 to 210/128
192/120 to 238/146	190/122 to 236/150
180/112 to 240/140	170/112 to 174/120
192/120 to 230/165	195/135 to 225/160
170/120 to 235/160	175/120 to 210/140
190/120 to 240/175	170/120 to 218/136
200/136 to 250/146	170/112 to 204/138
170/118 to 236/160	180/120 to 218/156

been greatly reduced by operation. It is probable that some of the symptoms associated with hypertension, such as headache, may occur only when the pressure reaches an excessively high level. Operation which may reduce blood pressure only slightly may lower it enough so that some of the symptoms do not occur. There seems no other logical explanation for the observation that relief of symptoms is much more marked than reduction of blood pressure in many instances. In most instances in which the blood pressure has been greatly reduced by operation headache is relieved, pain in the chest disappears, fatigue is lessened, and the patients gain weight and feel in general greatly improved. Many of them note diminution of nervousness and of a "let down" feeling, which gratifies them. Some patients have stated they feel "entirely well" or "better than in several years." In general, about 70 per cent of the entire group of patients were benefited

clinically. Some patients whose blood pressure has been greatly reduced by operation continue to note undue fatigue, weakness, and dyspnea for weeks or months after operation. One patient whose condition was followed closely did not regain normal strength until about six months after operation. We have not been able to determine definitely that the patients who notice these symptoms following operation are those who continue to have orthostatic hypotension but it appears that this is so.

Effect of Operation on Sweating.—The area of anhidrosis following operation is variable and not always equal in extent on the right and left sides. Extensiveness of anhidrosis depends on what part of the thoracolumbar sympathetic chain is resected at the time of operation. In the various cases studied the greatest area of anhidrosis begins at a line midway between the umbilicus and symphysis and extends distally.

Effect of Operation on the Heart.—When operation is successful, T-waves originally inverted in the electrocardiogram may become upright and the transverse diameter of the heart demonstrated by roentgen films exposed at 6 feet may decrease. Tachycardia occurs commonly when the patient stands after operation. When orthostatic hypotension is marked following operation, the increase in the pulse rate when the patient stands is also marked; 120 beats per minute is commonly observed and occasionally the cardiac rate is as great as 150 beats per minute when the patient stands. As time passes after operation, the increase in the rate of the heart when the patient stands decreases and the improvement parallels roughly decrease in orthostatic hypotension. However, tachycardia when the patient stands may persist after orthostatic hypotension disappears.

Effect on Renal Function.—Most of our patients who were operated on had no significant impairment of renal function; patients whose renal function was impaired were not operated on. Since we have not had opportunity to study the renal function of many of our patients after considerable time following operation has elapsed, and since tests for renal function when function is not significantly impaired are not always reliable for comparative purposes, we cannot say that renal function is improved following successful operation. Such an observation has been made by Freyberg and Peet.[6] It is quite apparent that renal function is not impaired when the blood pressure is greatly reduced by operation. This observation agrees with those of Freyberg and Peet,[6] of Page,[9] and of Page and Heuer.[10] Diminution in the amount of albumin in the urine or disappearance of it occurs commonly following successful operation.

Effect on Temperature and Motor Function of the Extremities.—Following operation the feet are warm and dry. If the blood pressure has been significantly decreased by operation the hands may be cold, apparently owing to persistence of vasoconstriction in these parts. An

occasional patient notes generally increased tolerance to warmth. The sensation and motor function of the lower extremities are not impaired. An occasional patient mentions an area of numbness, which is variable in extent in different cases and which is due to section of or traction on the lateral branches of the eleventh and twelfth intercostal nerves at the time of operation.

Effect of Operation on the Retinas.—The retinas of all our patients were examined by Dr. Wagener, an experienced ophthalmologist. The changes immediately following operation are not constant and cannot be correlated with the effect of operation on the blood pressure. The retinas of patients who are examined several months after operation, and whose blood pressures have not been significantly influenced, have not appreciably changed in appearance in most instances. In instances in which the blood pressure has been greatly reduced by operation, retinitis may disappear, and apparent sclerosis and arterial spasm may be greatly diminished. The cause of this is not entirely clear for reduction of pressure by extensive sympathectomy should not influence spasm of the retinal arteries as sympathetic control of them is not impaired, unless hypertension itself provokes arteriolar spasm or unless operation removes some mechanism which causes both. Again, if the results of the experimental work of Goldblatt[7] can be transferred to human beings with hypertension, it is possible that an increase of the renal blood flow may cause generalized decrease in arterial tonus, thus relieving spasm of the retinal arteries. It is also possible that retinal arterial spasm is compensatory, to prevent rupture in hypertension, and disappears when blood pressure is reduced. However, in spite of a significant reduction in blood pressure, examination of the retinas may disclose changes of the same degree as those observed preoperatively. These observations are in agreement with those of Fralick and Peet.[5]

Effect of Operation on the Intestines.—Disturbances of intestinal function were noted in a number of instances in which periods of three to four bowel movements daily, with stools of soft consistency, alternated with periods of normal bowel movements. In some instances constipation was relieved. Flatulence or other evidence of disturbed motor activity of the gastrointestinal tract were uniformly absent.

Effect of Operation on Sexual Function.—Ordinarily libido and erection are not impaired. However, some patients note diminished libido. Nocturnal orgasms occur as before operation but emission is usually absent or greatly diminished. Orgasm occurs normally during sexual intercourse but there is either no ejaculation of fluid or the amount is reduced. Male patients may be sterile after operation but this is not certain. Sexual satisfaction may be unimpaired or reduced. Menstruation occurs normally following operation and dysmenorrhea when present before operation may disappear following operation.

Effect of Operation on Basal Metabolism.—We have known for a long time that the basal metabolism is increased in many cases of essential hypertension. There is an almost uniform tendency for basal metabolism to be lower two to three weeks following the second operation than it was before operation. However, it is probable that several factors, such as prolonged rest in bed, anesthesia, operation and weakness contribute to reduction of the basal metabolism in addition to the diminution of blood pressure. In Table VI it is shown that of six

TABLE VI

EFFECT OF OPERATION ON BLOOD PRESSURE AND BASAL METABOLISM

(EIGHT ILLUSTRATIVE CASES)

BEFORE OPERATION		AFTER OPERATION*	
BLOOD PRESSURE	BASAL METABOLIC RATE, PER CENT	BLOOD PRESSURE	BASAL METABOLIC RATE, PER CENT
160/100	+14	140/90	+ 7
200/118	- 9	130/90	- 4
180/120	+ 1	112/80	-16
180/120	+ 9	140/100	+ 7
154/90	+12	116/72	+18
186/112	- 2	130/80	-11
150/110	+ 3	140/110	- 2
188/120	+11	160/120	- 5

*Two to three weeks.

instances in which there was substantial reduction of blood pressure following operation, in five there was reduction of basal metabolism. However, in two instances in which there was no substantial reduction of blood pressure by operation, the basal metabolism was decreased after operation. We hope to have further information on this interesting subject when we have had opportunity to determine basal metabolism considerable periods of time following operation.

Effect of Operation on Suprarenal Glands.—Although partial suprarenalectomy was a part of the surgical procedure in twenty-five instances, Addison's disease has never been observed. No significant changes in the amounts of sodium and chlorides in the blood, as results of operation, have been determined regardless of whether or not the suprarenal glands were partially resected. However, a regular increase in the amount of potassium, averaging 3 mg. in each, has been observed in eight cases, in five of which partial suprarenalectomy was not performed.

EFFECTS OF OPERATION ON BLOOD PRESSURE

As stated previously the results of operation for hypertension are not uniform; they vary from extremely poor to excellent. The results depend on selection of patients. At first patients were operated on who would not now be considered suitable for operation. The additional knowledge that operation for hypertension can be carried out with very little risk is further reason for surgical treatment of hypertension.

Whatever may be said about this procedure, it seems undeniably true that the patient is not harmed by it. The impression that some physicians have that operation itself leaves patients disabled and unable to carry on normal activities has no foundation in fact.

An analysis of the results of operation on this group of patients indicates that about 45 per cent of the patients operated on had no material change in blood pressure following operation (Table VII);

TABLE VII

EFFECT OF OPERATION ON BLOOD PRESSURE

(TWENTY INSTANCES OF POOR RESULTS)

BLOOD PRESSURE				
BEFORE OPERATION			AFTER OPERATION	
MAXIMUM	MINIMUM*	MEAN	PRESSURES†	MONTHS
205/130	160/110	180/125	192/122	19
210/130	150/105		210/130	14
190/140	130/100	180/130	235/180	18
215/150	170/115	180/130	215/150	16
220/140	140/105	180/120	170/124	17
220/155	180/115	200/120	190/120	16
250/180	160/120	220/150	220/135	10
208/160	160/90		215/150	14
220/140	140/100	180/110	170/130	9
230/160	180/112	200/130	180/130	9
210/150	160/110	180/130	190/130	7
230/140	190/115	200/126	200/130	6
250/140	190/100	170/100	200/120	7
240/160	210/110	220/130	220/170	8
140/190	208/170		Dead	7
210/135	150/90		200/125	6
230/154	180/130	200/134	190/130	6
220/130	170/120	195/125	214/130	4
175/120	140/95	164/112	180/120	10
252/145	200/110	220/115	252/134	6

*In this table and in Tables VIII and IX the term "minimum" applies to the lowest of twenty-four blood pressures determined hourly and consecutively while the patient rested in bed or slept.

†Rough mean in three determinations.

about 30 per cent received fair results in relation to blood pressure from operation and about 25 per cent received good results (Tables VIII and IX). With the methods of selection which we use now the incidence of failures is materially reduced. In Tables VII, VIII, and IX, it is shown that the minimal blood pressure resulting from rest and sleep before operation is a fairly good indication of the effects of operation on the blood pressure. It is well to emphasize again that errors in prediction of effects of operation on blood pressure are rarely made when preoperative tests indicate a poor result, but that errors of prediction occur occasionally when preoperative tests indicate a good result of operation. As a result of these observations we feel justified ordinarily in refusing to operate on patients when preoperative tests indicate that response of the blood pressure to operation will be unsatisfactory. We do not know that good results which follow operation will persist. Good results which persist for only several

TABLE VIII

EFFECT OF OPERATION ON BLOOD PRESSURE

(THIRTEEN INSTANCES OF FAIR RESULTS)

BLOOD PRESSURE				
BEFORE OPERATION			AFTER OPERATION	
MAXIMUM	MINIMUM*	MEAN	PRESSURES†	MONTHS
260/160	180/120		160/106	17
235/120	175/110		190/110	14
230/136	170/110	190/120	156/104	12
220/120	140/100	180/110	180/104	12
210/168	168/110	180/120	150/104	11
230/140	140/90	160/110	160/106	9
210/140	130/75		150/108	8
200/120	145/90	170/105	170/?	3
228/142	170/108	200/120	182/110	5
205/130	130/90		170/100	5
200/130	140/108	160/120	170/115	3
260/140	200/130	235/135	170/104	2
210/130	170/120		170/115	2

*,†see Table VII.

TABLE IX

EFFECT OF OPERATION ON BLOOD PRESSURE

(ELEVEN INSTANCES OF GOOD RESULTS)

BLOOD PRESSURE				
BEFORE OPERATION			AFTER OPERATION	
MAXIMUM	MINIMUM*	MEAN	PRESSURES†	MONTHS
205/135	140/100	160/110	150/90	23
225/130	150/100	190/110	128/90	15
240/105	130/95		160/90	15
190/135	140/90	160/114	140/100	15
180/114	144/90	174/110	150/90	15
240/140	145/100	170/120	128/80	14
220/150	170/120	190/130	140/100	13
205/120	175/90	200/110	165/95	10
200/135	150/90	180/114	140/100	5
220/140	146/78	230/150	140/?	3
210/130	150/92	170/110	140/78	2

*,†see Table VII.

months may justify operation, for patients are relieved of distressing and frequently disabling symptoms. For example, some patients feel that operations were worth while because of the relief of headache, if for no other reason.

CONCLUSIONS

1. The results of operation for essential hypertension can be predicted with reasonable certainty by observing the response of the blood pressure to rest and sleep, to ingestion of sodium amytal and sodium nitrate, and to intravenous injection of pentothal sodium. When poor results of operation are predicted as a result of these tests, the results are almost uniformly unfavorable. When good results are predicted, some patients do not receive as much benefit from operation as was anticipated.

2. There have been no operative deaths in a series of eighty-five cases. The operation itself does not disable, although anhidrosis of the lower extremities and loss of ejaculation and probably of fertility of the male result.

3. Following operation orthostatic hypotension and tachycardia occur but disappear as time passes.

4. Operation diminishes the response of the blood pressure to immersion of a hand in ice water.

5. Operation usually relieves symptoms when blood pressure is greatly reduced but may do so when there results no great reduction of blood pressure. About 70 per cent of patients were benefited clinically.

6. As a result of operation the heart may decrease in size, inverted T-waves in the electrocardiogram may become upright, retinitis and spasm of the retinal arteries may diminish or disappear, albuminuria may decrease, and renal function may be improved. The basal metabolism may be decreased.

7. The blood pressure was not materially reduced by operation in 45 per cent of this series of patients. Many of these patients would not be operated on now because preoperative tests would indicate that operation would not significantly reduce the blood pressure. About 30 per cent received fair results in relation to blood pressure and 25 per cent of them received excellent results.

REFERENCES

1. Adson, A. W., and Allen, E. V.: Essential Hypertension: I. General Considerations, Proc. Staff Meet., Mayo Clin. **12**: 1, 1937. II. The Rationale and Methods of Surgical Treatment, Ibid. **12**: 49, 1937. III. Selection of Patients for and Results of Surgical Treatment, Ibid. **12**: 75, 1937.
2. Adson, A. W., and Allen, E. V.: Essential Hypertension: General Considerations and Report of Results of Treatment by Extensive Resection of Sympathetic Nerves and Partial Resection of Both Suprarenal Glands, Proc. Inter-State Postgrad. Med. Assemb. N. Amer., p. 181, 1936.
3. Adson, A. W., Craig, W. McK., and Brown, G. E.: Surgery in Its Relation to Hypertension, Surg. Gynec. & Obst. **62**: 314, 1936.
4. Allen, E. V., Lundy, J. S., and Adson, A. W.: Preoperative Prediction of Effects on Blood Pressure of Neurosurgical Treatment of Hypertension, Proc. Staff Meet., Mayo Clin. **11**: 401, 1936.
5. Fralick, F. B., and Peet, M. M.: Hypertensive Fundus Oculi After Resection of the Splanchnic Sympathetic Nerves; a Preliminary Report, Arch. Ophth. **15**: 840, 1936.
6. Freyberg, R. H., and Peet, M. M.: The Effect on the Kidney of Bilateral Splanchnicectomy in Patients With Hypertension, J. Clin. Investigation **16**: 49, 1937.
7. Goldblatt, Harry: Experimental Hypertension Due to Renal Ischemia. Read at twenty-first annual session of American College of Physicians, St. Louis, 1937.
8. Hines, E. A., Jr., and Brown, G. E.: Cold Pressor Test for Measuring Reactibility of the Blood Pressure: Data Concerning 571 Normal and Hypertensive Subjects, Am. Heart J. **11**: 1, 1936.
9. Page, I. H.: The Effect on Renal Efficiency of Lowering Arterial Blood Pressure in Cases of Essential Hypertension and Nephritis, J. Clin. Investigation **13**: 909, 1934.
10. Page, I. H., and Heuer, G. J.: The Effect of Renal Denervation on the Level of Arterial Blood Pressure and Renal Function in Essential Hypertension, J. Clin. Investigation **14**: 27, 1935.

OBSERVATIONS ON PHLEBITIS*

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MUCH has been said on the subject of thrombosis and phlebitis, yet for the most part the etiology is still obscure and the treatment diversified and unsatisfactory. It is necessary to be skeptical of some of our so-called "fundamentals" until more data are secured. The observations here described are of diverse nature, and are not presented in any effort to arrive at conclusive deductions, but rather in the hope that they will arouse a critical viewpoint and lead to further clarification of our problem.

THE RÔLE OF INFECTION IN THROMBOPHLEBITIS

It may be of interest to examine the evidence in regard to the rôle of infection in the production of thrombophlebitis. In this respect phlebitis can quite easily be divided into two major groups, suppurative and nonsuppurative.

Suppurative phlebitis is seen in the immediate vicinity of a purulent focus, such as mastoiditis, septic endometritis, or carbuncle. It takes no special argument to establish the presence of infection in this form. The involved vein may not show any more clinical signs of inflammation than a bland phlebitis. The clot within it, however, is infected, and it undergoes purulent softening with a dissemination of bacteria and portions of clot throughout the blood stream. Wherever large enough masses of clot or bacteria block branches of the pulmonary artery, infarcts result, which go on to pulmonary abscess formation. Microscopic examination of the primary (autochthonous) portion of the thrombus shows the vein wall infiltrated with an exudate rich in polymorphonuclear leucocytes (Fig. 1). The bacteria are invariably found in this part of the vein and its contained clot. It may be noted that the *propagated* portion of the clot may be free of bacteria and the vein wall far from the original focus may show an exudate poor in polymorphonuclear leucocytes.

In the nonsuppurative category may be classed most of the cases of postoperative phlebitis, especially when it is not in the vicinity of the operative wound; as well as phlebitis of varicose veins, and finally the so-called "marantic phlebitis" occurring in fevers and in terminal states. At first glance such phlebitis might also seem to be a septic

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process. The involved vein is apt to be very hot and tender, and the swelling, augmented by phlebitic edema, may be considerable. Nevertheless the evidence for the presence of bacteria in this group is controversial and stands in considerable contrast to the clear-cut demonstration of bacteria in the septic variety.

The bland nature of nonsuppurative phlebitis had seemed well established by the work of Virchow.[1] With the advent of bacteriological examinations the picture was reversed. Vaquez,[2] in 1890, recorded the finding of micrococci in what had previously been called marantic thrombi, in patients dying of typhoid fever, tuberculosis, and even cancer. There are others who have searched for bacteria in these thromboses, and have also found them with fair frequency. Thus, Harris and Longcope[3] found bacteria in thirty-four out of forty-four cases of phlebitis, most of which were said to have been peripheral and of the so-called marantic type.

More recently deTakats[4] has gone a step further. Obtaining positive cultures in a goodly number of varicose veins removed at operation, he has formulated the concept of "resting infection" in varicose veins. According to this idea not only is varicose phlebitis an infective process, but the bacteria causing it may actually lie in varicose veins in a semidormant condition for long periods of time.

All these facts have gradually converted many physicians to the belief that all thrombophlebitis represents an infection of veins. In the meantime there has been rather strong evidence that nonsuppurative phlebitis is generally a bland process, and is rather due to physical factors such as slowing of the blood stream. Aschoff[5] is probably the most important contemporary proponent of this theory. This old theory gains modern support in the fact that several investigators have failed to find bacteria in most nonsuppurative phlebitis. Thus, Barker,[6] in a review of 166 cases of thrombophlebitis complicating infectious and systemic diseases, found that cultures were occasionally positive but usually sterile. Brown,[7] in a review of 87 cases of postoperative phlebitis, stated that no bacteria were found in those that were cultured. The reported results then, and my personal experiences, lead me to the conclusion that bacteria are only sporadically present in these cases.

So far as varicose phlebitis goes, my findings are somewhat paradoxical. While I have never been able to find bacteria by stain or culture of the clot or vein wall, I have nevertheless twice come upon gram-positive cocci in surgically excised saphenous veins, where there had been no suspicion of their presence. These patients did not have phlebitis, the wounds did not suppurate, nor was there evidence of any acute infection going on elsewhere in the body.

The histology of bland phlebitis differs also from that of the septic variety. There is usually very little cellular infiltration, and most of

the cells present are of the so-called "chronic inflammatory" or reparative type, that is, lymphocytes, plasma cells, and macrophages.* The infiltration may be located for the most part around the vasa vasorum in the adventitia. Polymorphonuclear leucocytes are uncommon and few in number. This holds true even in those cases where the phlebitis is attended by clinical evidence of acute inflammation with much heat, swelling, and tenderness (Fig. 2).

There is a form of phlebitis in which it seemed more probable to find bacteria and acute inflammatory cells. I refer to a subacute phlebitis of small veins on the foot which occurs occasionally in patients with varicose veins, especially those which have followed a deep phlebitis ("ulcerating phlebitis").[28] The special features of this phlebitis are the location below either malleolus, the immediate dark pig-

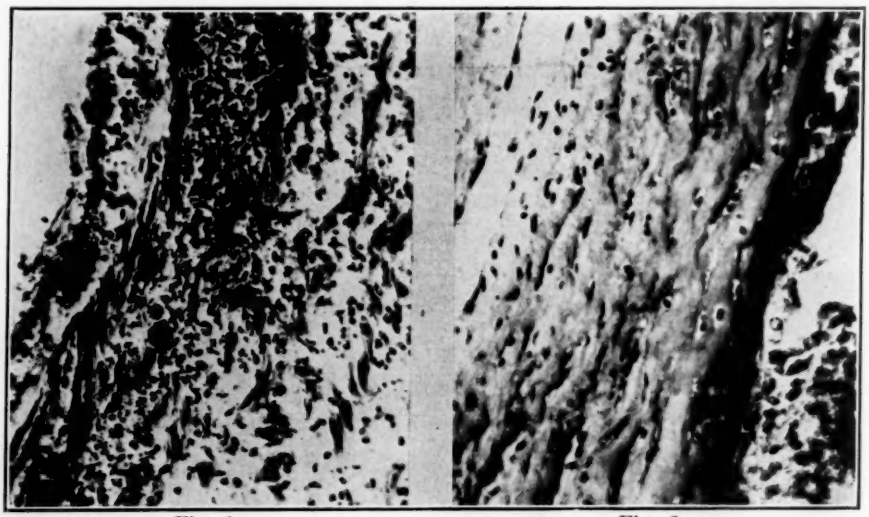

Fig. 1. Fig. 2.

Fig. 1.—Pylephlebitis, a septic phlebitis, secondary to suppurative appendicitis. Section of a branch of the portal vein in the liver. Note the intensive acute inflammation, the wall of the vein being disrupted by polymorphonuclear leucocytes. Eosin and methylene-blue (×190).

Fig. 2.—Phlebitis of a varicose vein, a bland phlebitis. Note the absence of inflammatory reaction. Hematoxylin and eosin (×190).

mentation of the skin over the vein, and its immediate adhesion to it; and finally the almost irrevocable breaking down of this skin into a shallow, painful, and intractable ulcer. In two such instances I have performed a biopsy of the vein and skin in the pre-ulcerous stage. Bacteriological culture was made at the time of the biopsy, but no bacteria were obtained by either aerobic or anaerobic methods. Nor were bacteria seen in stained sections of the veins and skin. The histology of the tissue was surprisingly mild, an organizing thrombus was present, with very little cellular infiltration. What cells were present were chiefly lymphocytes and plasma cells.

*The phlebitis of thromboangiitis obliterans stands out as an exception.

Evidence of the bland nature of most phlebitis is also to be found in its clinical course. Though frequently mentioned, suppuration of a thrombus in bland phlebitis such as that of varicose veins, is rare. Indeed, I have never seen a single instance. It is possible that softening of the clot through autolysis, has occasionally been mistaken for suppuration. Here also it may be noted that while pulmonary embolism is quite as common as in the septic form, the resultant infarcts do not give rise to pulmonary abscesses. Moreover, varicose veins which are phlebitic may be injected or ligated with safety. In 63 cases treated by ligation and subsequent injection not a single instance of sepsis of the vein or septicemia has occurred.

In the face of the evidence at hand the words of Welch,[8] spoken in 1909, are still convincing; "Whilst we are justified in assigning a far more prominent place to the agency of micro-organisms and to primary phlebitis in the etiology of thrombosis than, until recent years, has been customary since Virchow's fundamental investigations, recent attempts to refer all thromboses formerly called 'marantic' to the direct invasion of micro-organisms, and to phlebitis, go beyond demonstrated facts."

SYMPATHETIC NERVE IRRITATION ACCOMPANYING PHLEBITIS

Certain phenomena occur in the course of phlebitis which can only be explained by a stimulation of the sympathetic nerve fibers of the extremity. The mechanism is not yet known, but it is clear that whether the reactions are due to direct, or to reflex stimulation of the efferent fibers, irritation of a vein is an adequate stimulus for these reactions.

The simplest of these reactions involves the veins themselves. In some individuals the puncturing of a vein in the forearm causes an immediate constriction of all the superficial veins of the limb, and it is common experience that a second successful puncture may be impossible for some minutes. This same phenomenon may be seen in the leg when an irritant solution is injected for the purpose of obliterating varicose veins. Such a constriction has been described in phlebitis by Leriche,[22] and by Ducuing,[9] who believed it is responsible for much of the pain. There is additional significance in this, however, as the contraction of the vein slows the blood stream and facilitates the progress of the thrombosis.

Aside from venous constriction, we may consider a group of reactions which, while originating within the veins, spread to affect other structures. The first of these is the augmentation of the pilomotor reflex. Ducuing[10] has remarked that the reflex may be diminished or increased. In practice the diminution of this reflex is not easily made out, but its increase is sometimes strikingly apparent. Thus when both the normal and the diseased limbs are exposed in the patient's

room, the skin of the phlebitic limb may show a pronounced goose flesh appearance, while the normal limb shows it not at all or very slowly. Again, abnormal promptness and intensity of the reflex may be shown by scratching the limb with the back of the nails, when broad streaks of goose flesh appear.

The second function of the sympathetic fibers which comes in evidence is that of local sweating. While ordinary generalized sweat-

Fig. 3.—Localized sweating distal to tensely distended varices. The droplets were somewhat finer than shown.

ing occurs when the body is generally warmed, the local secretion can be seen even when the body is quite cold. This is the same type as that present in some neurological disturbances, in hyperhidrosis of the hands or feet and in those cases of vascular disease characterized by an increase in sympathetic tone. Well recognized examples of the latter are Raynaud's disease and thrombo-angiitis obliterans.

Localized sweating is frequent in the presence of vein irritation. It is best seen in cases of varicose veins that are large and tense or those

that are developing rapidly, as in pregnancy, and also in phlebitis of varicose veins. The sweat may only be apparent after the patient has been walking about or standing for some time. It appears as minute or medium-sized droplets arranged distal to the varices (Fig. 3). The droplets may be so small, indeed, as to be appreciated only on very close inspection or by feeling moisture on touching the leg. These droplets may increase in size, or make their first appearance, when the

Fig. 4. Fig. 6.

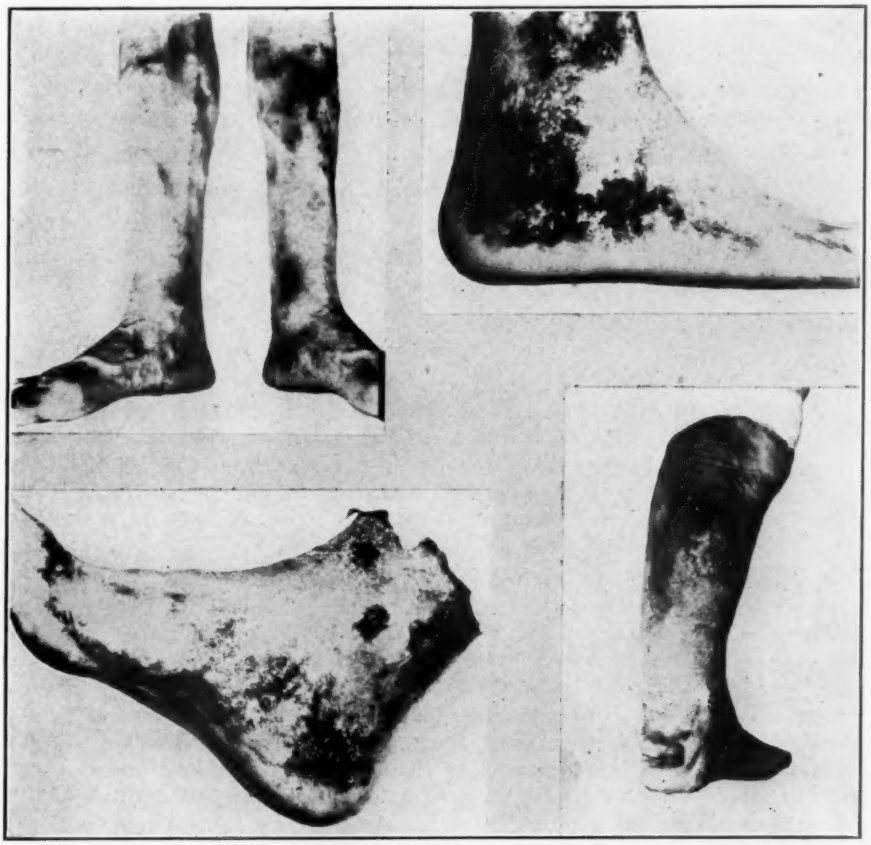

Fig. 5. Fig. 7.

Figs. 4 to 7.—Localized sweating in varicose veins and varicose phlebitis, outlined by starch iodine. Figs. 4 and 7 show proximal and distal areas. In each case the proximal area lies just below a zone of "phlebitis" induced by sclerosing injection. Fig. 5 is a case of varicose ulceration. Fig. 6 is of uncomplicated varices.

vein is punctured by a needle. The sweating is perhaps most apparent distal to areas of phlebitis in the varicose veins, whether it be spontaneous or induced by a sclerosing solution. To render the secretion conspicuous I have employed the starch iodine technique of Victor Minor.[11] A glance at the photographs of representative cases will show the fineness of the secretion and its localization into small areas (Figs. 4, 5, 6, 7). That the secretion is not necessarily an augmenta-

tion of the sweat in areas where it is normally high in amount, is shown by the fact that it is not confined to any one part of the leg or foot, but is called forth in any region distal to vein irritation.

Clinically the most important result of the sympathetic irritation is arterial constriction. It is quite commonly known that while, in phlebitis, the limb may be hot directly over the inflamed vein, it may be cold distal to it. Such a lowering of temperature can best be accounted for by a constriction of the arterioles.*

Examples of more severe involvement of the arteries have also been mentioned many times. Authors have often spoken of the small pulses in phlebitis. This diminution has been confirmed by the oscillometer in several reported cases, and in some personally observed ones.

Finally, phlebitis may occasion a complete spasm of the major artery of the limb. Twenty-odd such cases have been reported, the majority in the French literature, with others in the German and American.[13-20] The events in the reported cases resemble those in a personally observed one.

CASE REPORT

Mr. O. S., was seen on the Third Medical Service of the Boston City Hospital at the request of Dr. Cadis Phipps. This man, a forty-six-year-old carpenter, entered the hospital on July 19, 1935, for treatment of a pulmonary embolism resulting from a deep phlebitis of the right leg. Within the next two weeks, the phlebitis ascended to involve the right femoral, then the right iliac vein. On August 6, 1935, a series of events took place which were carefully observed and recorded by Dr. J. C. Druker, the House-Officer on service. I quote from his notes:

"August 6, 1935, the patient was seen at 9:00 A.M., and stated that he felt well except for some pain along the medial side of the left thigh. This pain in the left thigh was present for the first time. About 11:30 A.M. the patient was seen again and complained of more pain in this area and there was slight cyanosis of the left lower leg. The pulsation of the femoral artery was present and was of good volume. The patient also complained of some additional pain in the lower right chest (site of previous infarction). Examination of the chest showed no change from what had been heard previously; namely, diminished breath sounds at the extreme lower part of the right lung, posteriorly, and bronchial breathing which was distant above; and also a short terminal inspiratory friction rub anteriorly.

"At about 3:45 P.M. the patient complained that he was unable to feel any sensation in the left leg from the knee down and there was pain above this area. He complained also that he was unable to move the foot or toes. At this time, the leg from the hip down resembled in color an arm which has had a tourniquet applied in the tourniquet test for scarlet fever. The leg was cold, dry, and anesthetic up to the knee, while above, it was hyperesthetic. There were no pulsations made out in the femoral, popliteal, posterior tibial, or dorsalis pedis arteries.

"At about 6:00 P.M. hot water bottles were applied to the leg, and at 7:30 P.M. the condition of the leg from the knee down had changed considerably. The patient stated that ten minutes after the heat was applied, sensation had returned in the lower leg and in about three-quarters of an hour he was able to move the foot

*Audier[12] has found in these cases a more rapid absorption rate in the McClure-Aldrich test.

and toes. The leg was pink in color, sensation had returned, and there were good pulsations in the femoral, dorsalis pedis, and posterior tibial arteries. The femoral vein was palpable as a tender induration. Two enlarged veins were seen on the left flank which had definitely not been visible before.''

Comment.—This patient showed temporarily all the signs of an occlusion of the femoral artery; namely, the disappearance of the femoral pulse and the pulses below, the cold white skin, the anesthesia below and the hyperesthesia above, and the loss of muscle power. The diagnosis at the onset of this episode seemed surely to be either embolism or thrombosis of the femoral artery, yet with the application of heat, all the signs wore off and the pulses returned. Within a few hours the diagnosis of iliac and femoral phlebitis was definite. The limb subsequently went through the usual sequence that one finds in iliac phlebitis. There was edema from the buttock down; there was enlargement of the superficial veins of thigh and abdomen; and there was the tender induration of the femoral vein of the thigh. The edema slowly subsided during the patient's stay in bed. Later, when the patient was up and about, the edema increased temporarily but soon became less again.

By the latter part of September, 1935, there was but little edema and the surface veins of the thigh and abdomen were beginning to diminish in size, indicating that the clot was being canalized. The leg showed not the slightest evidence of arterial impairment. All the pulses were of full volume; an arteriogram showed that there was a normal lumen in both the main and deep femoral arteries; and the oscillometric readings (Pachon) were quite normal. The actual readings were as follows:

	MEAN ARTERIAL PRESSURE IN MM. OF MERCURY	OSCILLOMETRIC UNITS
Right thigh	120	6.5
Left thigh	120	6
Right leg	100	5
Left leg	100	5

In cases of embolism or thrombosis of the femoral artery, one must certainly have rare good fortune to observe the spontaneous reappearance of all the pulses of the limb and to find that the objective measurements of the calibers of the vessels are normal and exactly equivalent to the opposite extremity. As a matter of practice, such an outcome is but rarely observed, even after a successful embolectomy. One cannot escape the conclusion that this patient had no organic obstruction to the arteries at all, but that his arterial occlusion represented a temporary, complete spasm of the femoral artery, incident to the start of the phlebitis in the left iliac or femoral vein.

The picture then closely simulates arterial embolism. The femoral artery is the most frequently involved, and the spasm is secondary to

thrombophlebitis of the femoral or iliac vein. There is a sudden severe pain in the course of the artery, then in the entire leg. The femoral pulse is absent, the limb painful, cold, and paralyzed. After some few hours the attack may wear off spontaneously, or as has rarely happened, actual thrombosis may occur.

The arteriospasm may occur after the phlebitis is quite evident, but it usually happens so early that the diagnosis may be difficult to establish. Thus, while the telltale edema and cyanosis of phlebitis may be present, ordinarily the only hint of primary venous involvement is a slight cyanosis of the thigh above the ischemia of the foot and leg, and a slight dilatation of the surface veins of the thigh and abdomen.

In some of the earlier reports it is likely that there were included instances of a true arteritis by extension from pelvic sepsis, or simultaneous phlebitis and arteritis of thrombo-angiitis obliterans type. In many, however, there is no doubt but that there was merely a spasm of the artery.* Several of the reported cases were operated on for the suspected embolism. In all these the artery was found contracted and pulseless but the pulse reappeared immediately after the artery was freed from its sheath. In other patients arteriograms were made and the arteries found to be patent. Some of the patients died from pulmonary embolism and autopsy revealed patent arteries. Finally, gangrene occasionally supervened, and examination of the amputated extremities revealed normal arteries.†

CHANGES IN THE VENOUS VALVE

Apparently the fact that phlebitis damages the venous valve was first appreciated by Homans,[26] although he did not publish demonstrations of this damage. Recently, with Jesse Edwards, I have completed a detailed study of this effect. We made histological examinations of the valves in spontaneous phlebitis in the human and in experimental chemical phlebitis in the dog. This is reported elsewhere,[27] but it is of interest here to state briefly our findings.

When complete thrombosis occurs the forces of organization and recanalization pay little respect to the cellular nature of the valve, but treat it in the same way as they do the rest of the venous content, that is, the clot. In other words, the valve cusp is immediately subjected to disrupting forces. At first these forces consist of a growth

*The exact mechanism for the production of the arteriospasm is not known. Leriche,[21, 22] Homans,[23] and Jennings[24] have surgically explored the vascular sheath of the iliac and femoral vessels in some cases of phlebitis, and have occasionally found a nonpurulent plastic inflammation involving the adventitia of artery, vein and lymphatics, all with apparently equal virulence. Given such an inflammation, the spasm of the artery is explainable by direct irritation. In most instances, however, the vein is involved by itself and the artery is reflexly contracted. The possible path of such a reflex has been touched upon by Cornil, Mosinger, and Audier,[25] but has not yet been demonstrated.

Since this paper was written, de Takats (Arch. Surg. 34: 939, 1937) has reported vasospasm originating from phlebitis and other lesions and gives a fine discussion of the probable reflex arc.

†There are several reported cases of gangrene in the course of massive venous thrombosis, in which the arteries were demonstrated to be patent. In these cases, besides the extensive venous obstruction two other factors seem responsible, namely, spasm of the arteries and superimposed infection.

of capillaries through the base of the cusp and the exudation of reparative cells. But the fibroblasts, as they grow into the clot, cut across the cusp as well and divide it into fragments. At least some recanalization always occurs and the cusp is now more seriously fragmented by the new blood channels which run through it, and push its fragments apart. The cusp soon completely disappears. Occasionally the valve is open at the moment of thrombosis and its cusps therefore lie close to the vein wall. In such a case its fragmentation may be slight, but the cusp lies imbedded in the organizing thrombus and

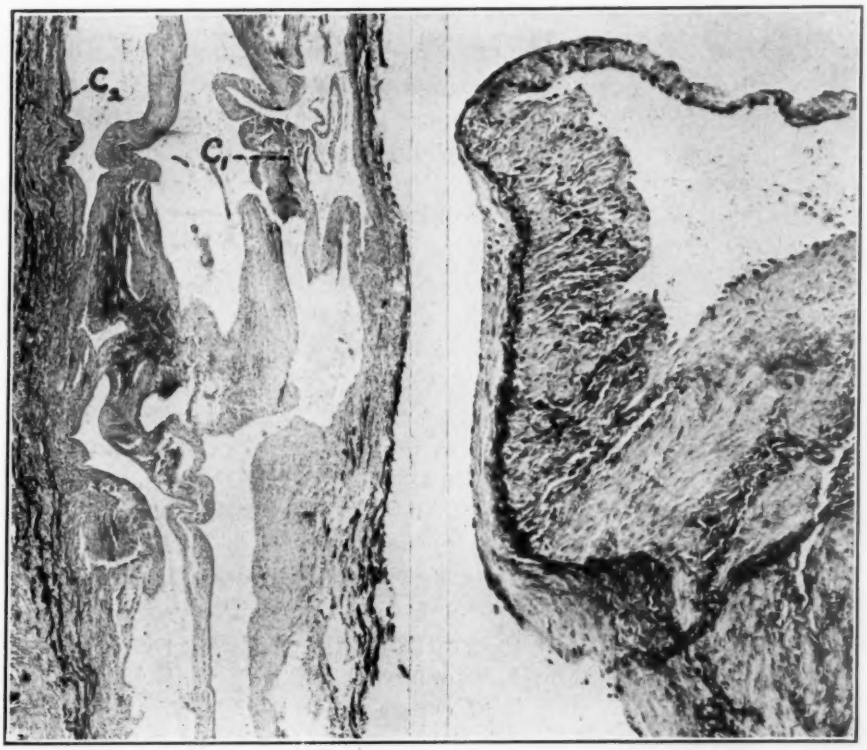

Fig. 8. Fig. 9.

Fig. 8.—Destruction of the venous valve by complete thrombophlebitis. Longitudinal section of dog's femoral vein at valve site, four months after artificial phlebitis. Recanalization is not yet complete but it has already broken up the thrombus leaving trabeculae crossing the lumen. In one of these, at *C-1*, is a small piece of elastic tissue, a remnant of the previously existing valve. At *C-2* is a longer strip representing the second cusp imbedded in the new thickened intima. The dark areas in the heavier trabeculae below are nuclei and pigment. Verhoeff's elastic tissue plus van Gieson's stains (×23.5). (From Surg. Gynec. & Obst. 65: 310, 1937.)

Fig. 9.—The production of venous stenosis and regurgitation by incomplete thrombophlebitis. Longitudinal section of single cusp from human saphenous vein involved in spontaneous phlebitis (operative specimen). The structure is thickened and shortened by the addition of connective tissue, especially on its sinus side. Here the connective tissue effects an adhesion of cusp to vein wall. Compare the thickness of the diseased proximal half of the cusps to the normal thin distal half. Verhoeff's elastic tissue plus van Gieson's stains (×92).

when recanalization is complete we find it incorporated in the now thickened intima. In any event, complete thrombosis always results in the actual or functional disappearance of the venous valve (Fig. 8).

Incomplete or parietal thrombosis, as is well known, has a predilection for attacking valve sites. The earliest thrombi are seen in the valve sinuses, where subsequent organization produces a pad of tissue which narrows the lumen of the vessel, and does not allow complete lateral excursion of the cusp. If the valve is open at the moment of thrombosis, with the cusp lying close to the vein wall, this organization incorporates it and it disappears in the new intima. If the valve is closed and the cusp lies in the center of the lumen, some of it will be bound down by the connective tissue formation in the sinus, and the remainder thickened by a proliferation of connective tissue along its two surfaces. This proliferation in the lateral commissure of the valve may also cause the two cusps to become adherent to each other.

The end-result of incomplete thrombosis is, then, a shortened, thickened, adherent cusp of little excursion (Fig. 9). These stubby, rigid valves look altogether different from the veil-like normal ones. The diseased valves resemble the mitral valve which has been involved in a rheumatic endocarditis, and we believe that the term "stenosis and regurgitation" may equally well be applied to both.

In the case of complete thrombosis of a main trunk we may see an incomplete thrombosis extending into the mouths of its tributaries. Here the valves which guard these mouths will be involved. The involvement may be of the type above described under the term "incomplete thrombosis" or there may be a special form of damage. In this latter instance the cusp as it opens into the lumen of the main trunk is caught in the thrombus of the main trunk. Here it may be destroyed if it is entirely embedded in the clot, or it becomes adherent along its free edge if it merely touches the clot. This is the type of involvement which destroys the function of the valves in the perforating vessels of the leg when a deep thrombosis occurs.

The destruction of the venous valve or the production of a venous stenosis and regurgitation helps to clarify the disability occurring after phlebitis. Reference is of course made to the so-called "post-phlebitic" evidences of inefficient return. Difficulty with the venous return exists whether or not the vein has recanalized. If the lumen is adequately restored the valves are absent or crippled. If it is not adequately restored, the blood flows in collateral channels, where, as we have indicated, the valves become incompetent due to the dilatation of these channels.

THERAPEUTIC INFERENCES

The management of phlebitis is undergoing considerable change. For the author, the essentially bland nature of the phlebitis of varicose veins and the almost absolute rule that both the varices and the phlebitis will recur after the acute process is over, have prompted the immediate treatment of these patients by ligation of the great saphe-

nous vein followed by small injections of sclerosing solution. Postoperatively the patient is treated in the same ambulatory fashion as any uncomplicated case of varicose veins. At the time of the first observation the thrombosis may make it impossible to determine whether or not the vein was valveless; but one may rest assured that it will be so when the recanalization has occurred. Therefore, whether or not the veins are surely varicosed, they are treated the same way, with the exception of cases of migrating phlebitis. These are treated conservatively because thrombo-angiitis obliterans is likely to be present. No pulmonary embolism or other untoward reaction has been seen in the 63 cases thus treated.[28]

The fact that phlebitis produces an irritation of the sympathetic fibers of the limb, leads one to inquire how this may be overcome and whether by so doing the patient will be benefited. Leriche and his associates[29, 30] have performed novocaine infiltration of the lumbar ganglia with immediate cessation of pain and subsidence of the edema. In the chronic postphlebitic edemas this procedure was only of temporary value. Other French workers have obtained good results by repeated subcutaneous injection of acetylcholine. The sympathetic release so obtained by these or any methods is undoubtedly responsible for the improvement noted. The increase in arterial flow thus obtained produces a greater velocity of flow in the veins, increasing their nourishment and diminishing the chances for propagation of the thrombus. If it is also true that venous spasm is a concomitant of phlebitis, its relief by sympathetic release will again increase the venous flow and inhibit the spread of the thrombosis. Appreciating the presence of sympathetic irritation should make us question the use of cold applications in phlebitis. The use of the ice pack has already fallen into disrepute with many, because it promotes thromboses and devitalizes tissue. Now we have this additional reason for condemning it.

Though the above methods of securing vasodilatation deserve extension, I have so far been content to use local warmth in the form of a heated cradle, or as hot compresses, while in the severer cases I have used parenteral foreign protein. Such therapy, as you know, diminishes the coagulability of the blood and lowers the sympathetic tone. Striking results have followed the use of intravenous typhoid vaccine, or in sicker patients the intramuscular injection of sterile milk products.

Of late the matter of rest and exercise in phlebitis has also attracted some attention.[31, 14, 32] Previously, patients with either superficial or deep phlebitis were kept in bed for weeks or months in order to minimize activity of the limb and thus cut down the chances for pulmonary embolism. The thrombus at the original site of the phlebitis is more or less fixed because of the changes in the vein wall, antecedent or secondary, but there is frequently a propagation of

softer more friable clot attached to either end of the original thrombus. This clot is due to the stagnation of the blood and has therefore been called a "stagnation thrombus." These propagated clots are not necessarily in contact with vein wall all along their course, and no amount of time may suffice for them to become firmly attached. Sooner or later the patient must move his limbs, in bed or out, and if stagnation thrombi have formed they are practically sure to break off and to give embolism.

It has been amply demonstrated, in superficial phlebitis at least, that immediate exercise of the limb will prevent the formation of this secondary clot from which emboli arise. Deutsch, in 1929,[33] and Jaeger, in 1930,[34] reported six hundred, and one hundred cases, respectively, of superficial phlebitis of the leg, treated merely by bandaging and forced to remain ambulatory. In these consecutive cases not a single pulmonary embolism resulted.

Confronted with a deep phlebitis, it is more difficult to fly in the face of custom and to prescribe exercise. If the phlebitis has lasted for some days with the limb at rest, stagnation clots are already apt to be present. Certainly at this stage very active exercise is dangerous, but it seems logical that there is even more chance for pulmonary embolism if the stagnation is continued, than if regular gentle movement be instituted. If the patient has survived a single pulmonary infarct, he may die from a second or third. For this reason, whenever feasible, the main venous trunk should be ligated after pulmonary embolism.

If the phlebitis is fresh, my feeling is that gentle exercise of the limb should be started at once and be increased daily. The results in several cases thus treated have been gratifying. Pulmonary embolism is, however, such a serious accident, that a large series of phlebitics treated both with and without exercise will have to be compared before this can be laid down as the best method of procedure.

REFERENCES

1. Virchow, R.: Zur Geschichte der Thrombose, Wien. med. Wchnschr. 7: 217, 1857.
2. Vaquez, H.: La Thrombose Cachectique, Thèse, Paris, 1890.
3. Harris and Longcope: Quoted by Welch.[8]
4. deTakats, G.: "Resting Infection" in Varicose Veins: Its Diagnosis and Treatment, Am. J. Med. Sc. 184: 57, 1932.
5. Aschoff, L.: Thrombosis, in Lectures in Pathology, New York, 1924.
6. Barker, N. W.: Thrombophlebitis Complicating Infectious and Systemic Disease, Proc. Staff Meet. Mayo Clin. 11: 513, 1936.
7. Brown, G. E.: Post-operative Phlebitis. A Clinical Study, Arch. Surg. 15: 245, 1927.
8. Welch, W. H.: Thrombosis, in Allbutt and Rolleston's System of Medicine, Vol. VI, London, 1909.
9. Ducuing, J.: Quelques Signes Neuro-Sympathique des Phlèbites Post-opératoires. Leur Valeur dans le Diagnostic Précoce de cette Affection, Prat. méd. franç. 14: 222, 1933.
10. Ducuing, J.: Le Rèflexe Pilo-motor dans le Diagnostic Précoce des Phlèbites Post-opératoires, Bull. Soc. d'obst. et de gynéc. 22: 255, 1933.

11. Minor, V.: Ein neues Verfahren zu der klinischen Untersuchung der Schweissabsonderung, Deutsch. Ztschr. f. Nervenh. **101**: 302, 1928.
12. Audier, M.: Le Test D'Aldrich et McClure dans le Diagnostic des Phlébites des Membres, Gaz. méd. d. France, p. 18, April 1, 1934.
13. Homans, J.: The Operative Treatment of Phlegmasia Alba Dolens, New England J. Med. **204**: 1,025, 1931.
14. Homans, J.: Thrombophlebitis, in Nelson's Surgery, Vol. III.
15. Läwen, A.: Arteriospasmus bei akuter massiver Thrombose der V. femoralis, Zentralbl. f. Chir. **56**: 1,681, 1934.
16. Wertheimer, P., and Frieh, P.: Thromboses Veineuses, Obliterations Artérielles, et Gangrène des Membres, Presse méd. **43** (1): 1,004, 1935.
17. Audier, M.: La Symptomalogie Artérielle dans le Phlèbites des Membres et de leurs Sequelles, Progrès. méd., May 4, 1935, pp. 729-738.
18. Audier, M.: Thromboses Veineuses Aigués simulant L'Embolie Artérielle des Membres, Paris méd. **1**: 384, 1936.
19. Gutzeit, R.: Brand durch Venensperre, München. med. Wchnschr. **83**: 1,628, 1936.
20. McKechnie, R. E., and Allen, E. V.: Sudden Occlusion of the Arteries of the Extremities, Surg. Gynec. & Obstet. **63**: 231, 1936.
21. Leriche, R.: Essai de Traitement Chirurgical des Suites Eloignées des Phlébites du Membre Inférieur, Presse méd. **27**: 309, 1923.
22. Leriche, R.: Traitement Chirurgical des Suites Eloignées des Phlébites et des Grands Oedemes non Médicaux des Membres Inférieurs, Bull. et mêm. Soc. nat. de chir. **53**: 187, 1927.
23. Homans, J.: Phlegmasia Alba Dolens and the Relation of the Lymphatics to Thrombophlebitis, AM. HEART J. **7**: 415, 1932.
24. Jennings, J. E.: Choked Leg, Ann. Surg. **98**: 928, 1933.
25. Cornil, L., Mosinger, P., and Audier, M.: Les Interrelations Arterio-Veineuses Pathologiques des Membres, Presse méd. **22**: 411, 1937.
26. Homans, J.: The Operative Treatment of Varicose Veins and Ulcers, Based Upon a Classification of these Lesions, Surg. Gynec. & Obstet. **22**: 143, 1916.
27. Edwards, E. A., and Edwards, J. E.: The Effect of Thrombophlebitis on the Venous Valve, Surg. Gynec. & Obstet. **65**: 310, 1937.
28. Edwards, E. A.: Phlebitis of Varicose Veins. To be published.
29. Leriche, R., and Kunlin, J.: Traitement Immediat des Phlébites Post-Operatoires par L'Infiltration Novocainique du Sympathique Lombaire, Presse méd. **76**: 1,481, 1934.
30. Kunlin, J., and Lucinesco, E.: Résultats du Traitement Immédiat des Phlébites Post-Operatoires et Variqueses par L'Infiltration Novocainique du Sympathique Lombaire. Cinq. Nouvelles Observations, Bull. et mêm. Soc. nat. de chir. **61**: 965, 1935.
31. Kilbourne, N. J.: Phlebitis. Its Treatment, California & West Med. **45**: 176, 1936.
32. Ochsner, A.: Thrombophlebitis. In Dean Lewis' Practice of Surgery, Vol. XII.
33. Deutsch, H.: Zur Behandlung der akuten lokalizierten Phlebitis der unteren Extremität, Wien. klin. Wchnschr. **42**: 1,162, 1929.
34. Jaeger, F.: Zur Behandlung der Thrombose und der Thrombophlebitis, Zentralbl. f. Chir. **57**: 1,921, 1930.

THE PATHOLOGICAL BASIS FOR INTERMITTENT CLAUDICATION IN ARTERIOSCLEROSIS*

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THE symptom complex of intermittent claudication, or exercise pain, which may occur in any type of obliterative or obstructive arterial disease of the lower extremities, is a common though by no means a constant concomitant of arteriosclerosis. In some cases it occurs before any other definite vascular symptom is manifest. In other cases gangrene of the toes or the foot supervenes from gradual arterial occlusion, or from trauma and infection, without the appearance at any time of the syndrome of intermittent claudication.

Arteriosclerosis is a disease in which vasospasm and infection are absent, at least from the initial picture, and in which the basic pathological change is a purely obliterative process affecting the arteries. Why intermittent claudication should be present in some cases and not in others, or, indeed, why it should occur at all, is not clearly understood. It is generally believed that its basic cause is the diminution in the blood volume which reaches the involved part as the result of arterial obstruction, but thereafter the theories of its causation vary. Lewis,[1] in an excellent monograph entitled "Vascular Disorders of the Limbs," advances the idea that the cause is obstruction of the large vessels of the extremities. Hermann,[2] on the other hand, recognizes two forms of obstruction of the arterial supply which might produce it, obstruction of the large trunks and obstruction of the arterioles. The only work on record, so far as we know, which concerns the anatomical distribution of the points of obstruction or obliteration in this symptom complex was done by the author,[3] and records the vascular pattern in 12 cases of intermittent claudication on an arteriosclerotic basis.

The valuable experimental work of Barney Brooks[4] has thrown considerable light upon the altered physiology produced by obstruction of the large arteries. Three important changes occur, he says: The blood volume flow is diminished, the intravascular pressure is decreased, and the pulse pressure is markedly diminished or disappears entirely. Brooks found, furthermore, that even a slight decrease in the flow of blood to the extremity produced a fatigue complex comparable to intermittent claudication. He therefore concluded that the diminution in the blood volume was the main factor in the production of intermittent claudication.

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By means of arteriography we have been able to carry Brooks' observations farther. All our studies show that when the large arteries of the extremities are suddenly obstructed, whether by trauma, severance of the vessels, or thrombosis, there is a diminution in the number of functioning smaller muscular arteries and their terminal branches, and, undoubtedly, closure of many of the arterioles and capillaries in which these arteries terminate.

Before going into further detail on this subject, it may be well to outline briefly our experience with arteriography, by which method, during the past five years, we have had the opportunity of studying many types of peripheral vascular diseases of the lower extremities. The technique for visualizing the vessels of the lower thigh, popliteal region and upper two-thirds of the leg we have outlined in other communications[5, 6, 7] and shall not repeat here. At the beginning of our work, we made, for purposes of comparison with pathological cases, a series of arteriograms of the blood supply in normal cases in various age groups, and by the study of these arteriograms we established certain criteria for the normal blood supply:

1. The femoral, popliteal, and tibial arteries with their branches present a smooth, regular course. They decrease in size as they progress toward their termination, but at no point is there any narrowing of the channel by plaques or other types of obstruction.

2. The large muscular branches are given off uniformly from the large trunks and are long and evenly distributed.

3. The small muscular branches are numerous and are given off at regular intervals from the larger branches. They terminate in fine twigs, which in turn supply even finer twigs to all parts of the soft tissue. The whole process may properly be described as arborization, and the picture is precisely the picture seen in the branches of a tree. All parts of the muscular tissue are uniformly supplied, and the terminal twigs literally cover the entire muscular area (Fig. 1*A*).

4. The hallmarks of a normal vascular supply may be set down as smoothness of contour, regularity of pattern, and adequacy of size and distribution.

In arteriosclerosis there are several distinct patterns of arterial obliteration, which vary widely in extent. In one group of cases there is a gradual narrowing of the large trunks, with a variation in the development of the collateral blood supply. Sometimes the development of new vessels has kept pace with the obliterative process in the large trunks, so that obstructive symptoms never develop: when the large trunks have been completely occluded, an adequate collateral circulation has taken over their function. Sometimes the obliterative process outstrips the development of the collateral circulation and serious obstructive symptoms are manifest early. At other times the collateral circulation takes the form of large, tortuous vessels, which seem to carry an adequate volume of blood to the extremity, yet which actually do not,

as serious obstructive symptoms promptly supervene. In another group of cases the large trunks may remain patent and the obliterative process may be confined chiefly to the smaller vessels; in such cases serious symptoms of obstruction are always present. In the final group of cases the obliterative process involves uniformly the entire arterial system of the extremity, and marked symptoms are of course inevitable.

Our present communication is based upon an analysis of the vascular changes, as demonstrated by arteriography, in a series of 41 cases in which intermittent claudication was the outstanding symptom, and in all of which the basic vascular pathology was arteriosclerosis. In most cases other signs and symptoms of vascular degeneration were present in addition to the exercise pain, and in eight cases gangrene of one or more toes was also exhibited. There was a wide variation in the duration and severity of the exercise pain. In some instances it appeared when the patient had walked less than a block, while in other instances the patient could walk as much as ten blocks before it appeared. In all patients the pain was typical, in all it affected the calf muscles, and in almost all it was bilateral. The period of rest necessary for relief varied from one and one-half to fifteen minutes.

The age range in this group was from thirty to seventy-five years, with the average age 51.4 years. White males predominated, followed in order of frequency by white females, negro females, and finally negro males. The series of cases is obviously too small to make deductions from these findings of any value.

All the pictures were made in the basal state, that is, during a rest period, and at room temperature, in order to rule out the effect of exercise or of increased local temperature on the vascular picture. All pictures were taken so that the entire pattern was visualized at the site at which pain was most pronounced. In other words, all the arteriograms showed the lower femoral and popliteal arteries and the arteries of the upper two-thirds of the leg. The pictures were studied first by normal standards, and then in comparison with each other, in order to determine both variations from the normal and changes in the vascular pattern common to all cases. To simplify the comparisons we divided the arterial system of the extremity into its component parts, these including: the lower femoral artery; the popliteal artery; the anterior tibial artery; the posterior tibial artery with its main branch, the peroneal; the large muscular branches; and the secondary muscular branches with their terminal twigs, which latter were studied with the aid of a magnifying glass.

Our findings fall into three distinct groups, some of which are further subdivided:

1. In 21 cases there was complete obstruction at some part of one of the large trunks;

A. In five cases the lower femoral artery was obstructed. In four of these the lumen of the popliteal artery was narrowed, but the vessel

filled from a collateral supply; in the other case the obstruction extended through the popliteal artery. In all five cases the tibial arteries and the peroneal were patent and were filled from collateral vessels.

B. In twelve cases the popliteal artery was obstructed. In eight of these cases the upper portions of the posterior and of the anterior tibial artery were obstructed, as was the popliteal artery; in the other four cases these arteries were patent throughout. The tibial vessels were usually filled at a lower level by communicating branches.

C. In four cases there was a marked narrowing of the femoral and the popliteal arteries, with obstruction of the anterior tibial artery in five cases and of the posterior tibial and the peroneal arteries in one case.

2. In six cases there was a definite, marked narrowing of the lower femoral and the popliteal arteries, although in no instance was the obstruction complete. Sometimes the constriction was uniform, sometimes large atheromatous plaques protruded into the lumen, producing almost complete obstruction at these points.

The collateral circulation in these cases varied considerably. Sometimes several large collateral vessels originated above the obstruction of the popliteal artery and extended well down into the calf muscles. Sometimes the attempt at the formation of a collateral circulation was very slight. Sometimes collateral vessels extended the whole length of the leg and undoubtedly carried a sufficient volume of blood to the extremity; the muscle fibers, however, did not receive adequate nutrition, since the new collateral vessels provided no small muscular branches.

In all the cases in which one or more of the large trunks was completely obstructed or markedly narrowed, it was striking to note the diminution in the number of functioning muscular branches. This was particularly evident in the smaller branches, and some arteriograms showed large areas of muscle devoid of any small muscular branches.

3. In fourteen cases the large vessels of the extremity were patent throughout their course and their lumina were within normal range. Sometimes their course was tortuous, but there were no points of constriction or obstruction. Here the defect was in the small muscular branches, which were few in number, irregularly distributed, and considerably shorter than normal. There was also a marked diminution in the number of fine terminal branches given off from the muscular branches. This group of cases, we feel sure, is usually described as arteriolosclerotic, and it is important to note that the obstruction involves the small muscular branches, as well as the arterioles and capillaries.

It is clear from what has been said that the single abnormality common to all these cases is the obstruction of the small muscular branches with their fine terminal twigs (Fig. 1), or, to put it differently, the loss of the arteriolar and capillary arborization by means of which the muscle fibers are supplied. This is the only abnormality present in the third group of cases, and it is present also in the first two groups, in

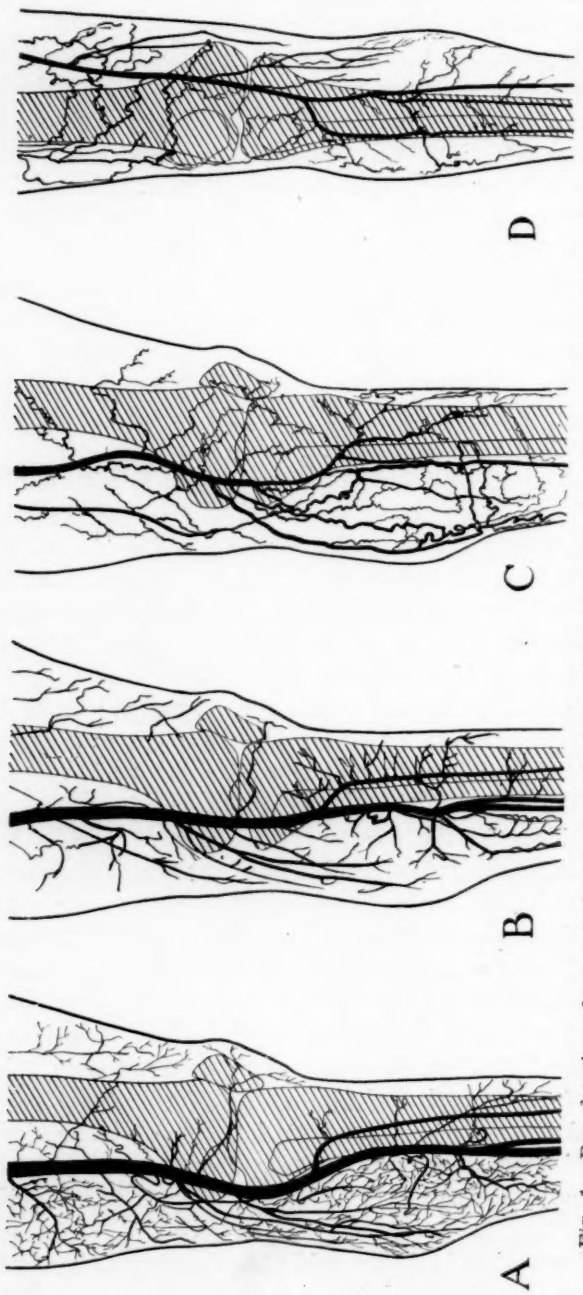
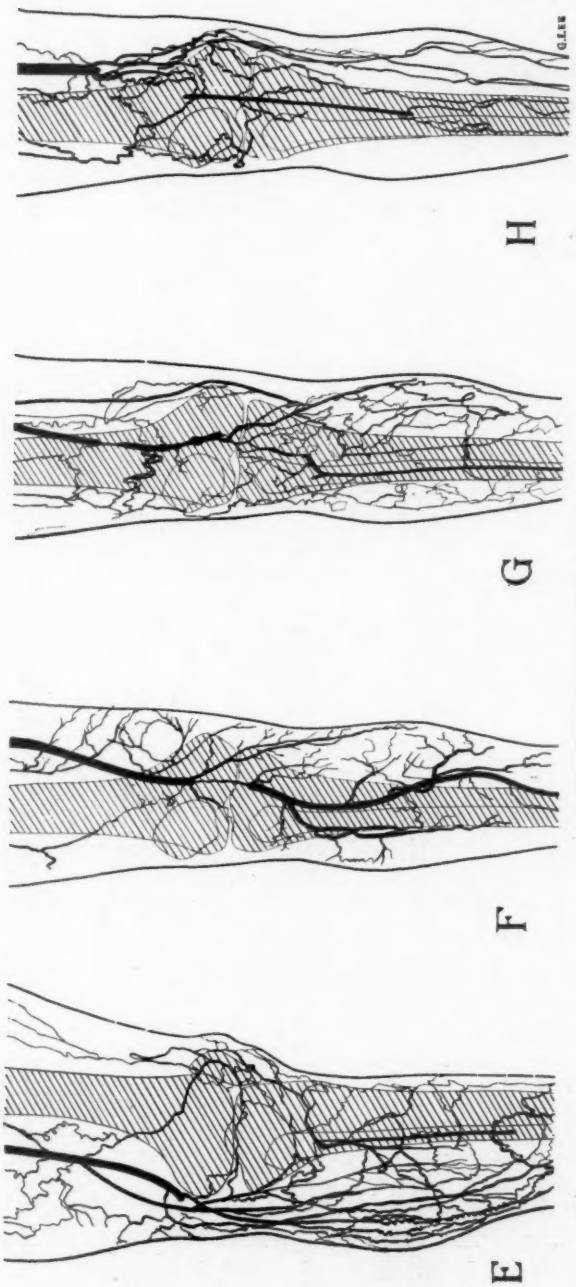


Fig. 1.—Pen drawings from arteriograms of the lower thigh and upper two-thirds of the leg. *A* shows the normal arterial pattern and *B*, *C*, *D*, *E*, *F*, *G*, and *H* show variations from the normal in arteriosclerotic types of intermittent claudication. Note the uniform distribution of the smaller nutritional arteries in the normal pattern (*A*), and the decrease in number and irregular distribution of these vessels in pathologic cases.



H

G

F

E

(See legend on opposite page.)

which there is complete obstruction or some degree of narrowing of the large trunks. Our studies show that the obliterative process may affect all the muscles of the extremity, or a single muscle, or even an isolated portion of some muscle.

Further proof that it is the obliteration of these fine vessels which is responsible for the impairment of muscle function is supplied by repeated arteriographic studies on patients whose intermittent claudication has improved under treatment. In such cases we have never noted

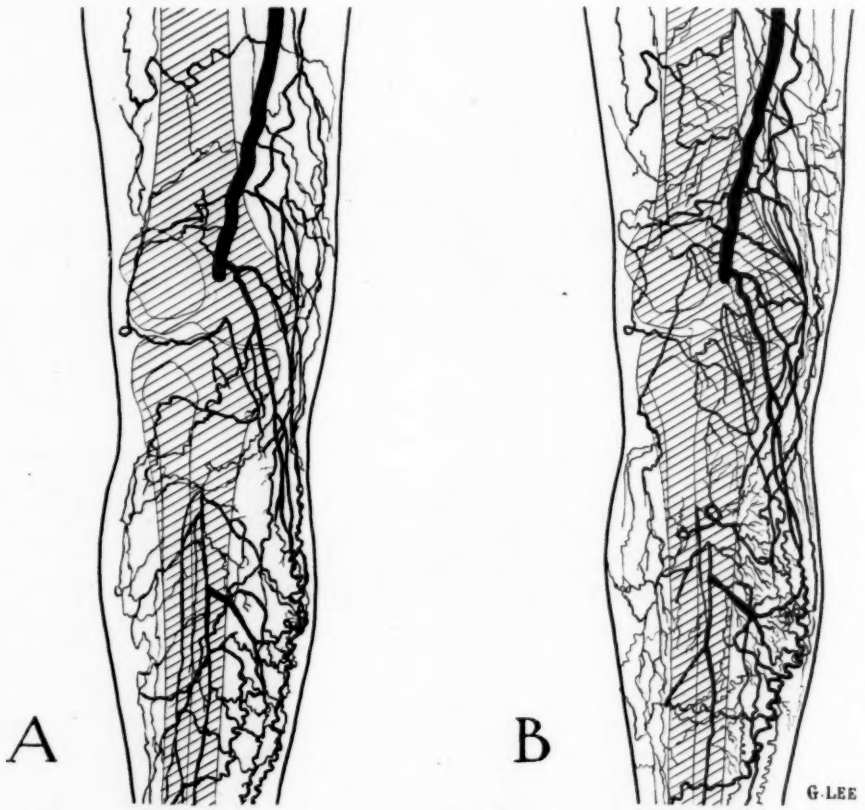


Fig. 2.—*A*. Case of intermittent claudication before treatment, showing obliteration of the popliteal artery. Note the extensive development of the collateral circulation and the diminution in the small muscular branches. *B*. The same case after relief of the intermittent claudication by treatment with alternate suction and pressure therapy. Note the marked development of small muscular branches and terminal twigs.

any change in the large vessels, but we have invariably noted an increase in the number and size of the fine terminal arteries, as well as an improvement in their distribution (Fig. 2*A* and *B*). We have also seen cases in which arteriosclerotic gangrene of the foot was present, with complete obstruction of the popliteal artery (Fig. 3), but in which exercise pain was absent because, we believe, the development and distribution of the small muscular branches was adequate.

The vascular patterns in intermittent claudication which we have outlined are the patterns seen during the resting stage, at which time there is no pain. It is now necessary to consider the changes which occur in the arterial supply during exercise, when there is pain.

In a previous communication[3] on this subject we have shown that during the exercise or pain period in arteriosclerotic intermittent claudication there is actually more blood flowing to the extremity than there is during rest; the increased volume flow occurs because many small

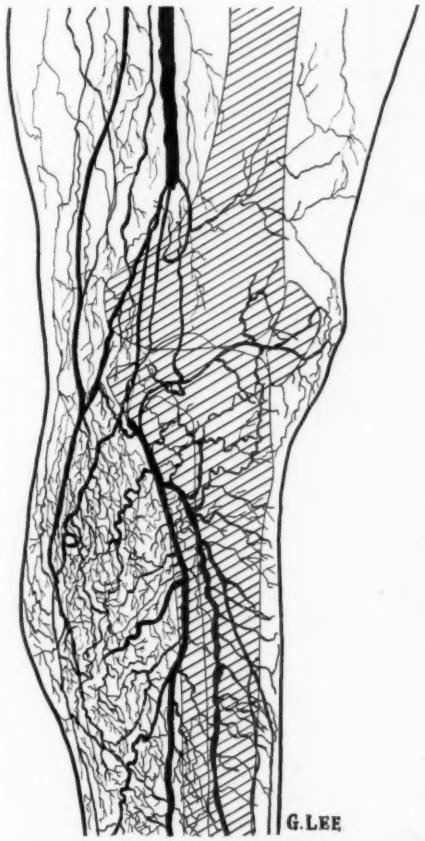


Fig. 3.—Case of gangrene of the toes, with complete obliteration of the popliteal artery. Intermittent claudication is not a symptom, presumably because the development of small muscular branches (which note) has resulted in a sufficient volume of blood to the muscles.

vessels are called into play by the exercise. It may therefore be assumed that patients with intermittent claudication react to exercise as do normal individuals, though to a more limited degree.

It is the abnormal distribution of the blood supply and the inaccessibility of certain portions of the muscles which produce impaired nutrition. There seems no reasonable doubt that the vascular changes which we have outlined impair the nutrition of muscle fibers. There is always, as

we have pointed out, a diminution in the volume flow of blood to the various muscles, and there are areas of muscle fiber in which the arterial supply is completely obliterated. These fibers, however, although deprived of their immediate arterial supply, do not die promptly, as would be expected, since they receive nutrition through the tissue spaces from the venous circulation.

Tissue cells, it must be remembered, do not come directly into contact with the arterial or venous blood. They receive their nutrition from tissue space fluid or lymph, which is derived from both the arterial and the venous circulation and which, various physiologists[8] have shown, can be altered by obstruction of either of these circulations. Obstruction on the arterial side produces a diminished lymph circulation, while obstruction on the venous side, or increased venous pressure, leads to an increased lymph flow. Nature has provided such a margin of safety between these circulatory systems that slight changes in either produce no pathological results. If there is only a slight change in the arterial flow, there will be a compensatory change in the venous flow to overcome it. An increased arterial flow causes a more rapid venous flow, a slowing or decreased arterial output causes a decrease in the rate of venous flow, so that the venous channels are kept filled.

Normally the volume of arterial blood passing through the capillaries into the venous system is sufficient to keep this system well filled. With exercise there is a tendency to empty the veins with each contraction of the muscles, while with each muscular relaxation the veins are promptly refilled. In arterial obstruction, when there is a lowering of the intraarterial pressure and a marked diminution in the number of functioning small muscular branches, arterioles and capillaries, smaller quantities of blood reach the venous system, which therefore fills more slowly. During exercise the venous system is repeatedly emptied, and when the muscle relaxes there is always some delay before the venules and veins are refilled. During rest the tissue space fluid is adequate for the nutrition of the muscle fibers; during exercise, on the other hand, the venous blood is emptied from the vessels and the tissue space fluid is correspondingly depleted.

The experimental work of Lewis and his co-workers[9] might be quoted in this connection. The theory which they have advanced to explain the pain of intermittent claudication is based upon an elaborate set of experiments dealing with the production of ischemic pain by obstruction of the arterial supply. On the basis of this work they conclude that pain is caused by a product of muscular metabolism, which they term factor P. The background, so to speak, is an inadequate blood supply to the muscles of the parts, the inadequacy being evident only during exercise. When successive muscular contractions occur, the state of the muscle undergoes a progressive alteration, and, as this alteration takes

place, its product, the hypothetical factor P, is given off and collects in the extramuscular tissue spaces. Factor P, which is a physicochemical product, with a cumulative action, is given off during exercise, they believe, even when the blood supply to the muscle is adequate, but under these circumstances it does not rise to the pain level in the tissue spaces. In other words, although obstruction to the blood supply is the essential basis of the pain, the pain stimulus itself, the hypothetical factor P, is a product given off by the muscle fibers.

Lewis' theory is ingenious, but obviously, until factor P has been isolated, it must remain only a theory. It is true, furthermore, that he was dealing with complete obstruction of both the arterial and the venous systems in normal muscles. On the other hand, it cannot be questioned that the pain in such circumstances is similar to the pain of intermittent claudication in arteriosclerosis, and we are inclined to accept his views, except in one respect. In arteriosclerosis, one is dealing with an arterial obstruction and the venous system is presumably patent. During rest the veins supply an adequate amount of lymph to the muscle fibers. During exercise, however, the tissue space fluid is necessarily depleted. This is because, as the result of the lowered blood volume, the veins which empty during the contraction of the muscles in the period of exercise are not promptly refilled during the period of relaxation. As exercise continues and this cycle is constantly repeated, the tissue space fluid becomes more and more depleted. With the depletion of the tissue space fluid, an altered metabolism occurs in the muscle fibers, and an acute starvation, so to speak, exists. The result is that abnormal metabolites, such as the hypothetical factor P of Lewis, are produced, and pain results. As the veins are refilled during rest, the tissue space fluid is replaced, the abnormal metabolites are washed away, the normal cellular metabolism once again takes place, and, as a result, the pain subsides.

REFERENCES

1. Lewis, T.: Vascular Disorders of the Limbs, New York, 1936, The Macmillan Company.
2. Hermann, L. G.: Passive Vascular Exercises, Philadelphia and London, 1936, J. B. Lippincott Company.
3. Veal, J. R., and McFetridge, E. M.: Vascular Changes in Intermittent Claudication, Am. J. M. Sc. **192**: 113, 1936.
4. Brooks, B.: Pathologic Changes in Muscles as a Result of Disturbances of Circulation, Arch. Surg. **5**: 188, 1922.
5. Veal, J. R., and McFetridge, E. M.: Technical Considerations in Arteriography of Extremities With Thorotrast, Am. J. Roentgenol. **32**: 64, 1934.
6. Idem: Arteriography in Gangrene of Extremities by Use of Thorium Dioxide (Thorotrast): Study Based on Twenty-Seven Cases, Ann. Surg. **101**: 766, 1935.
7. Idem: Adequate Circulation in Extremities; Arteriography as Test for Determining Its Limits; Preliminary Report Based on Thirty Amputations, J. A. M. A. **104**: 542, 1935.
8. Starling, E. H.: Principle of Human Physiology, Philadelphia, 1930, Lea & Febiger.
9. Lewis, T., et al.: Observations Upon Muscular Pain in Intermittent Claudication, Heart **5**: 359, 1931.

INTERPRETATION OF ARTERIAL ELASTICITY FROM MEASUREMENTS OF PULSE WAVE VELOCITIES*

I. Effect of Pressure

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IN THE study of cardiovascular disease a considerable body of knowledge of the physiological behavior of the heart and the small vessels of the periphery has accumulated. The large arteries have, however, received only moderate attention in this regard and yet it is clear from the number of studies devoted to their pathological state that their importance for the circulation is well recognized. The relatively small number of studies concerned with their physiological state is due rather to the lack of accurate and direct methods than to lack of interest. Knowledge of the function of the vascular system as a whole cannot, however, be said to be complete without information as to the behavior of the larger arteries.

Essential hypertension has been rather extensively studied with regard to the action of the heart and the peripheral arterioles. No fact seems clearer than that peripheral resistance is increased in this disease and that this increase is due to constriction of the arterioles.[1, 2, 3] Information as to whether this increase in tone is confined to the muscular coat of the arterioles alone, or whether it extends throughout the musculature of the entire arterial system might then be of assistance in analyzing the mechanisms involved. The chief function of the arterioles is, perhaps, regulation of the flow of blood, and in order to quantitate the function one studies the latter. Similarly, the principal function of the large muscular arteries, aside from the very obvious one of acting as conduits, is dependent upon their ability to stretch, that is, upon their elastic properties. One studies, therefore, their elasticity.

Hypertension was chosen for study because, as just stated, much is known about other parts of the circulatory system and especially because it affords, in the early stages at least, opportunity to study temporary or functional changes in the walls of the arteries. During the progress of this work, valuable information upon this particular point has been published by Haynes, Weiss, and Ellis[4] and by Weiss, Haynes, and Shore.[5] Although the data in the two studies are somewhat similar, differences in mode of analysis and in interpretation of results have made the continuance of work in this laboratory seem important.

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The method of measuring elasticity of arteries in the intact animal depends upon the close relation which exists between the speed of the pulse wave in, and distensibility of, an artery. The relation was first set forth in detail by Moens in 1878.[6] It is exact but is unfortunately somewhat complex in that a number of factors in addition to the elastic state of the wall affect the speed of transmission. The subject has been recently and thoroughly reviewed in an excellent study of the relation of age to elasticity of the arteries by Hallock,[7] and for this reason only a brief statement concerning the points pertinent to the present subject is necessary. It is plain from Moens' equation (Fig. 1*A*) that the speed of the arterial pulse wave depends upon at least four variables, one of which is the elastic state of the arterial wall. If other variables could, then, be kept constant or in some way accounted for, an accurate estima-

A

$$V = \sqrt{\frac{g \cdot Ea}{\Delta \cdot d}}$$

g = gravity
E = coefficient of elasticity of the wall
a = thickness of wall
Δ = Sp. Gr. of blood
d = diastolic diameter of artery

B

$$V = \frac{3.57}{\sqrt{\%\text{ increase in volume per mm. Hg. increase in pressure}}}$$

Fig. 1.—(*A*) Moens' and (*B*) Bramwell and Hill's equation relating velocity of propagation of the arterial pulse wave to elastic properties of the arterial wall.

tion of the elasticity of the artery might be made. Unfortunately, this is not the case. Variables must be eliminated or their effects measured by all the means at our disposal, and even then their elimination is only partly successful.

Let us consider these variables successively and discuss what may or may not be done with each.

(1) The specific gravity of the fluid (blood) in the tube varies relatively very little and may, for present purposes, be supplanted by a constant factor.

(2) The diameter of the artery and thickness of its wall cannot, obviously, be measured directly in the intact organism. It is therefore necessary to compare observations made upon the same artery when attempting to evaluate variations in elasticity. Even so, arteries are known to change their diameter and thickness of wall by contracting or

relaxing the muscular coat. It is clear, however, that by changing muscular tone, elasticity is also altered. The observed change in velocity of propagation of the pulse wave is due partly to change in size of the artery and partly to change in elasticity. Bramwell and Hill[8] in 1922, recognizing this fact, transformed Moens' formula so that it involved only speed of the pulse wave and pressure within the artery (Fig. 1*B*), permitting calculation of the pressure-volume curve for any given speed in a particular artery. They showed clearly that error due to thickness of wall and diameter was, in any one artery, small. It must be borne in mind however that the equation does not distinguish between the part played by the thickness of the wall and the diameter of the artery from that part played by the constitution of the wall. The curves obtained in this way are simply a measure of the sum of these effects upon the elasticity of the artery and not necessarily of the elastic state of the walls alone. Change in speed of the pulse wave due to change in state of the arterial wall and change in caliber of the artery seem, still, to be inseparable.

(3) Perhaps most important of all the variables which relate speed of pulse wave to elasticity is the pressure within the artery. It is important not only because it exerts a great effect upon the speed of the pulse wave but also because its physiological variations are rapid, frequent, and large. Pressure, as such, does not appear in Moens' formula but is of course implicit in the elastic coefficient E which is a ratio of volume to pressure. All observers agree, however, that change in pressure is not proportional to change in volume in such a way as to agree with Hook's law. The coefficient of elasticity is therefore not a constant —it is a variable dependent, for one thing, upon pressure.

Some notion of the magnitude of the effect of pressure upon the distensibility of the arterial wall may be obtained by considering a curve of increase in volume for successive increments of pressure (Fig. 2) derived from a curve relating speed to pressure in an excised artery. It is plain that much greater force is required to obtain the same degree of distention at high than at low pressures. It is, consequently, necessary to know at what pressure the elasticity of the artery is being measured before drawing conclusions concerning the state of the wall.

When velocity is used as an index of distensibility the pressure at which it is measured is, then, important. The problem becomes, in the intact animal, which pressure is important—systolic, diastolic, or mean? Obviously it is the pressure at which the pulse wave is transmitted and this is, in intact animals, diastolic pressure, since velocity of the pulse wave is customarily calculated by measurements made upon the first upstroke of the pulse wave, i.e., the one which begins at the diastolic level of pressure. Wiggers[9] has shown that the pressure waves produced at systolic level travel at much higher speeds than those ordinarily

recorded for pulse wave transmission. Frank[10] has demonstrated that reflected waves do not appear upon the pulse wave soon enough to disturb the initial upstroke beginning at diastolic levels of pressure at least as far as the radial and femoral pulse is concerned. In spite of the fact that logic compels acceptance of the dependence of velocity of the pulse wave upon diastolic pressure, many workers continue to attempt to relate the velocity of the pulse wave to systolic pressure, mean pressure, and pulse pressure. And if one keeps clearly in mind that speed can have only an indirect relationship with these levels of pressure the procedure may well be useful.

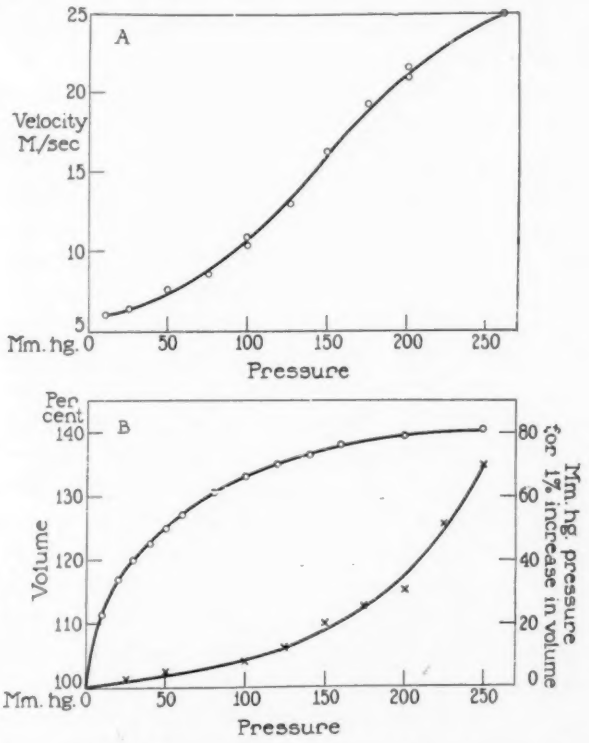

Fig. 2.—(*A*) A curve of the relation found to exist between speed of transmission of the pulse wave along, and pressure within, the normal brachial artery excised from the arm of a man aged forty years, eighteen hours after death. (*B*) The curve joining the points marked × is calculated from the equation of Bramwell and Hill and shows the increase with pressure of the force required to produce a given increase in volume; the one joining the circles illustrates the progressively declining increase in volume for each successive increase in pressure.

But the usual reason for correlating the pulse wave velocity with various pressure levels appears to be that in dealing with large groups of individuals most authors[11-15] have been unable to find correlation with the diastolic level. The reason for this will be made clear in a few moments. First it seems advantageous to describe several experiments in intact dogs designed to alter systolic without altering diastolic pressure, and the reverse, in order to test separately their effect upon

velocity of the pulse wave. This step seems necessary because as Weiss and collaborators also have pointed out confusion exists in medical literature as to which level of pressure is the important one.

The method of Bramwell and Hill[8] employing two hot wire sphygmographs connected through Wheatstone bridges to two galvanometers and by stiff rubber tubes to two tambours in contact with the iliofemoral artery of dogs (Fig. 3) was used to measure the interval of time between the arrival of the pulse wave at two distant points along the artery. A cannula leading to a Frank manometer was placed in the internal iliac just at its emergence from the iliofemoral artery. Three methods were employed for changing one level of pressure without the other: First, partially clamping the aorta just above the proximal tambour was found within certain limits to reduce systolic without altering, significantly, diastolic pressure; second, an arteriovenous shunt through artificial peripheral resistance just beyond the distal tambour allowed some variation of diastolic without noteworthy change in systolic pressure. Two examples will suffice to illustrate their use. The first (Fig. 4) illustrates not only the effect of clamping the aorta but also the constancy of the preparation in the absence of any meddling. The four parts of the record were obtained during a period of thirty minutes. When the aorta was severely clamped (*C*) the systolic pressure dropped sharply without materially affecting the pulse wave velocity or the diastolic pressure. Otherwise the record is quite constant. Combinations of both methods are shown in the second example. In *A* (Fig. 5) the aortic clamp is in place, wide open, the arteriovenous shunt closed, in *B* the aorta has been compressed to roughly one-third or one-half the cross section. Systolic pressure has fallen sharply, neither diastolic pressure nor the velocity of the pulse wave has changed significantly and do not change with removal of the clamp and consequent return of systolic pressure to its previous level. When, with aortic clamp open, the artificial arteriovenous aneurysm or shunt is opened, the diastolic pressure in the artery falls 20 mm. Hg, and the pulse wave velocity decreases from 10.7 to 8.5 M./ sec., whereas the systolic level is not materially affected. Now when the aortic clamp is again applied (*D* and *E*) systolic pressure falls rapidly while diastolic pressure and velocity of the pulse wave both increase slightly. With release of the aortic clamp (*F*) the systolic pressure returns to its former level but not until the arteriovenous shunt is closed (*G*) do diastolic pressure and pulse wave velocity follow suit.

The third procedure employed for changing one level of pressure without the other was to cut the leaflets of the aortic valve by thrusting a barbed hook sheathed in a long cannula until its arrival at the valve down the left carotid artery through the valve and withdrawing it. An enormous fall in diastolic pressure can in this way be induced without any drop, in fact with a rise, in systolic pressure. Velocity of the pulse wave

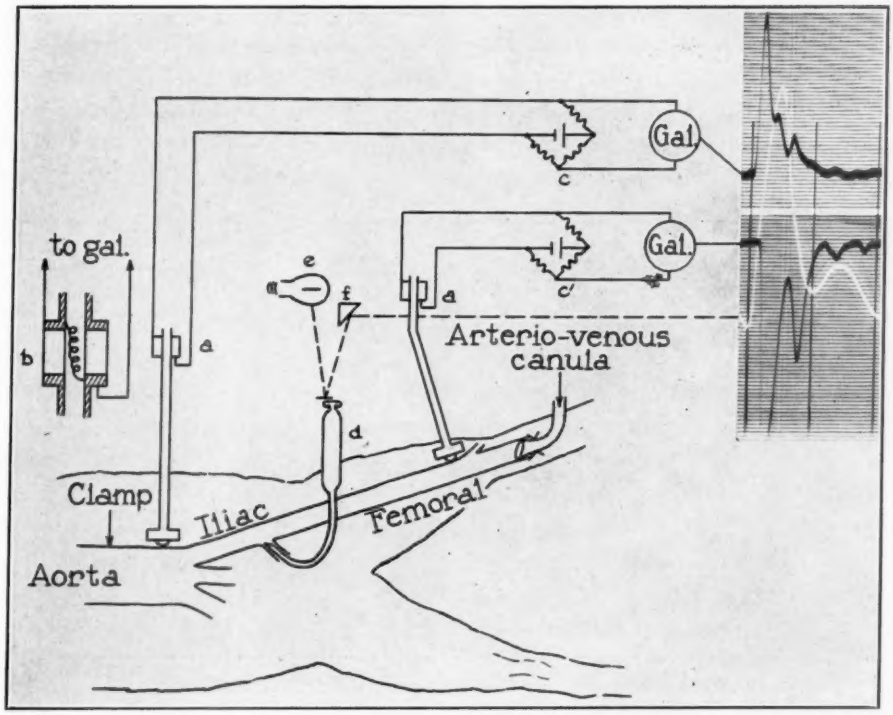

Fig. 3.—A diagram is shown of the arrangement of apparatus for obtaining simultaneous records of pressure within and speed of transmission of the pulse wave along the iliofemoral artery of dogs. *a*, *a*, hot wire sphygmographs; *b*, sphygmograph enlarged; *c*, *c*, Wheatstone bridges; *d*, Frank capsule and cannula in the internal iliac artery; *e*, source of light; *f*, prism.

The inset in the right hand upper corner is a reproduction of an actual record. In this figure and in Figs. 4, 5, and 6, the black curves are written by the two galvanometers, and from the difference in time between the upstroke of one and the downstroke of the other the velocity of the pulse wave is calculated. The curve written in white is the record of pressure obtained by the Frank capsule.

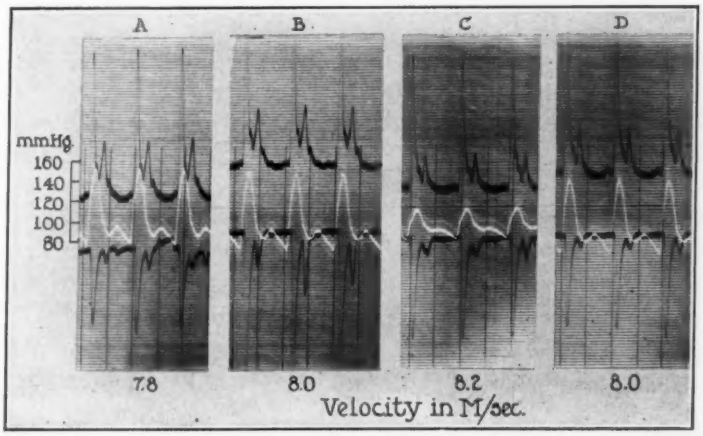

Fig. 4.—Simultaneous records of pulse wave velocity and pressure obtained from the iliofemoral artery of a dog are shown. *A*, *B*, and *D* before and after, and *C* during application of an aortic clamp.

parallels closely the changes in diastolic pressure without relation to either systolic or mean pressure. A single example is given (Fig. 6). Before cutting the valve, the systolic level was during a fifteen minute period (*A*) about 158, the diastolic approximately 118. The velocity of the pulse wave varied from 7.7 to 8.0 M. / sec. (*A*). One cusp was then completely cut through and a small hole torn in another (as shown by

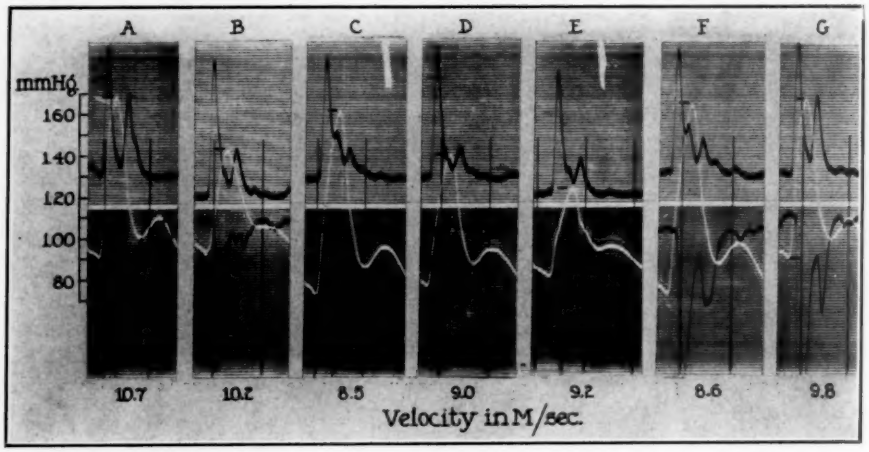

Fig. 5.—Simultaneous records of pulse wave velocity and pressure obtained from the iliofemoral artery of a dog are shown. *A* with aortic clamp and arteriovenous shunt in place, clamp open, shunt closed; *B* with the aorta partially clamped, shunt still closed; *C*, *D*, *E*, and *F* arteriovenous shunt open, *C* and *F* aortic clamp open, *D* and *E* two stages in the closure of the aortic clamp; *G* as in *A*.

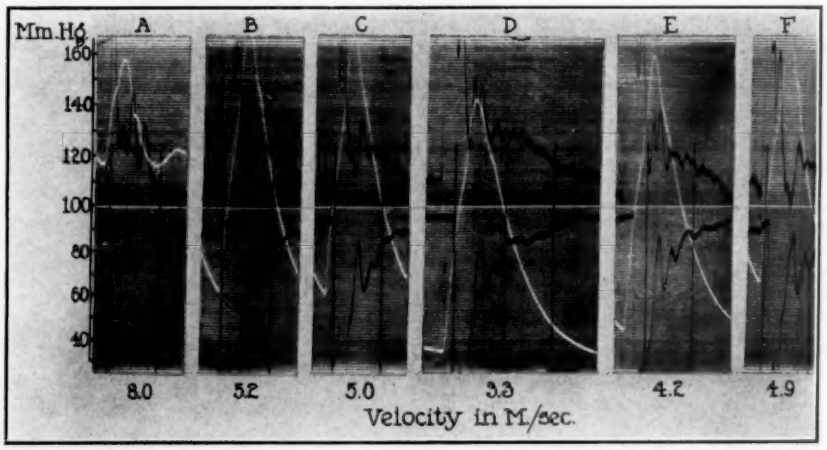

Fig. 6.—Simultaneous records of pulse wave velocity and pressure obtained from the iliofemoral artery of a dog are shown. *A* control; *B* and *C* after cutting aortic valve; *D* after slowing by vagal stimulation; *E* partial recovery from vagal stimulation at a time when systolic level has returned to its original level (compare *A*); *F* complete recovery from stimulation, i.e., similar to *B*.

subsequent examination of the heart). Systolic level rose slightly, diastolic pressure fell abruptly and with it velocity of the pulse wave (*B* and *C*). When in addition the vagus was stimulated to slow the rate, diastolic pressure and pulse wave velocity both fell much farther. Dur-

ing this period there was also a drop in systolic pressure (*D*) but a record taken during recovery from stimulation (*E*) secures a point in time when systolic pressure has reached the original level while diastolic pressure and velocity remain at one-half their original values. Plainly velocity follows the diastolic level. In the last record (*F*), the state immediately after section of the valve has again been reached.

These observations strongly reinforce the logical argument that velocity of the arterial pulse wave depends, so far as it depends on pressure at all, unequivocally upon diastolic level.

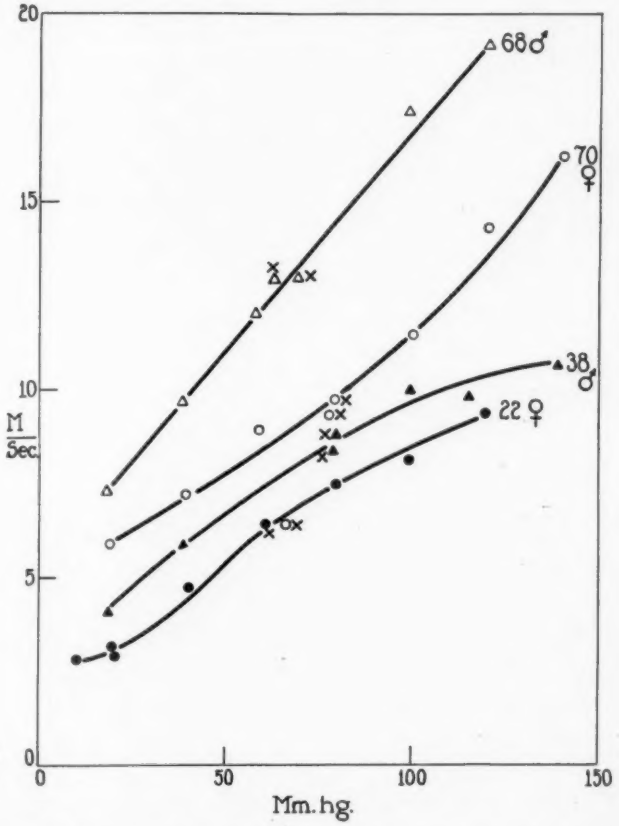

Fig. 7.—Curves describing the relation of pulse wave velocity to diastolic pressure obtained in the brachioradial arteries of four normal individuals are shown to illustrate variability among individuals. The observations obtained at the naturally existing pressures are marked by ×.

With the knowledge that speed of pulse wave varies with diastolic pressure in accordance with prescribed laws, the effect of pressure upon the speed of the pulse wave in the brachioradial artery in normal individuals and in individuals suffering from hypertension was studied. If diastolic pressure is the one upon which the speed of the pulse depends, the methods of Bramwell, McDowall, and McSwiney[16] and Hem-

ingway, McSwiney, and Allison[17] for altering the *effective* pressure within an artery can be considered as altering essentially diastolic pressure. The method consists in measuring the speed of the pulse wave while a known portion of the arm between the two points selected for recording the arrival of the pulse waves is subjected to various external pressures. From these measurements the speed of the wave at various diastolic pressures in the region so treated can be calculated and pressure-speed curves constructed for each subject.

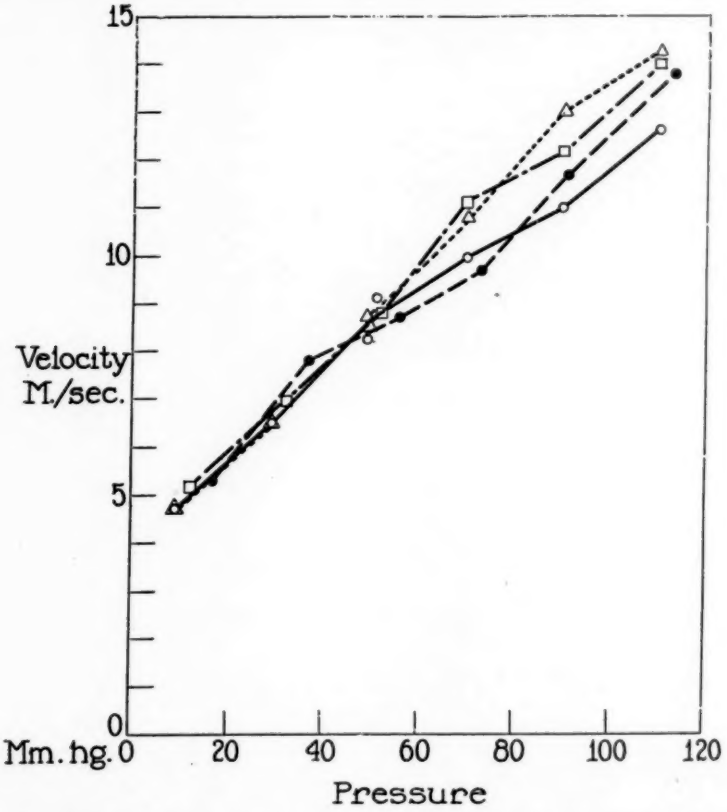

Fig. 8.—Four curves are shown relating pulse wave velocity and diastolic pressure obtained from one individual at intervals during a period of six months to illustrate individual constancy.

From such curves (Fig. 7) the velocity of pulse wave at any pressure may be calculated by reading off the velocity recorded at the intersection of the curve with the ordinate representing the desired pressure. That individual curves are necessary for calculating the velocity of each subject at a particular pressure is to be expected from the great differences between individual relationships noted by Hemingway, McSwiney, and Allison[17] and found also in the present series. Four are shown as examples (Fig. 7).

The velocity of the brachioradial pulse wave was measured in 48 normal individuals whose ages varied from thirteen to ninety-one years at the natural diastolic pressure and then a curve of the pressure speed relations was constructed for each individual in the manner just described. In 20 subjects from two to five curves were constructed for each. In contrast to the great differences between individuals the curve of a particular individual varies but little from week to week (Fig. 8). The velocity at 80 mm. mercury was then calculated for each individual. When the whole group of velocities naturally observed is plotted against age it is readily seen that speed of the pulse wave increases with age as has been repeatedly shown. And if the velocities are calculated at 80

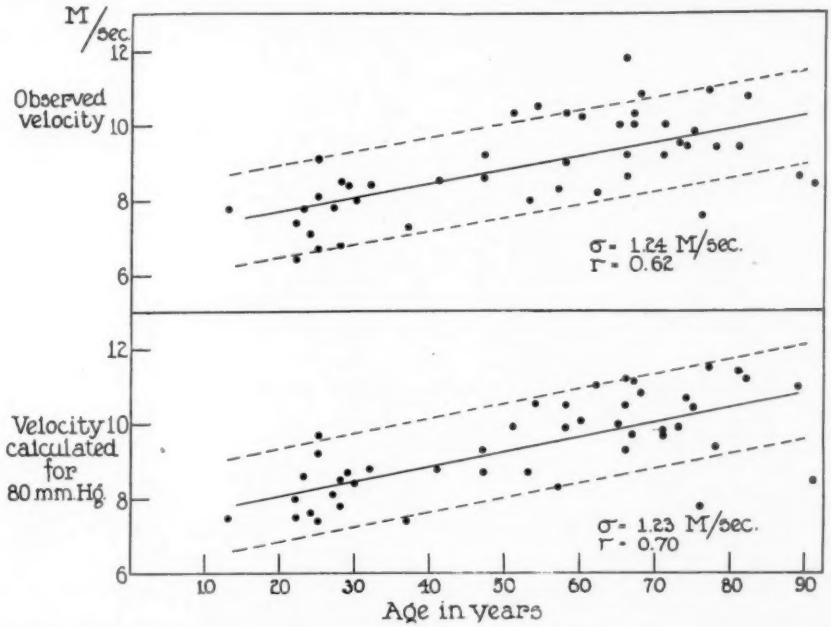

Fig. 9.—Velocities of the pulse wave in the brachioradial arteries of forty-eight normal individuals are plotted against age; above are the velocities obtained at natural diastolic pressures, below are those calculated in the manner described in the text at 80 mm. Hg. In this figure and in Fig. 10, the solid lines represent the regression equations, the dotted ones, the standard error of estimate.

mm. Hg and plotted in the same way, it becomes plain that adjusting them for diastolic pressure has not had an observable effect (Fig. 9). The standard deviation is one and a quarter meters and correlation with age is highly significant in either case (0.62 and 0.70). Correlation with diastolic pressure is not significant just as most workers have found. The reason for lack of significant correlation is probably due to the fact that the observed range of variation in diastolic pressures in normal people is plainly too small to bring out correlation with velocity in the presence of the much larger variations in velocity found to occur from one

individual to the next. The standard deviation of diastolic pressure is 10.2 mm. Hg. A change of 10.2 mm. Hg in the average individual would change the velocity of the pulse wave roughly only 0.4 and 0.6 of a meter or one-third the standard deviation of the velocity of the pulse wave at a given age.

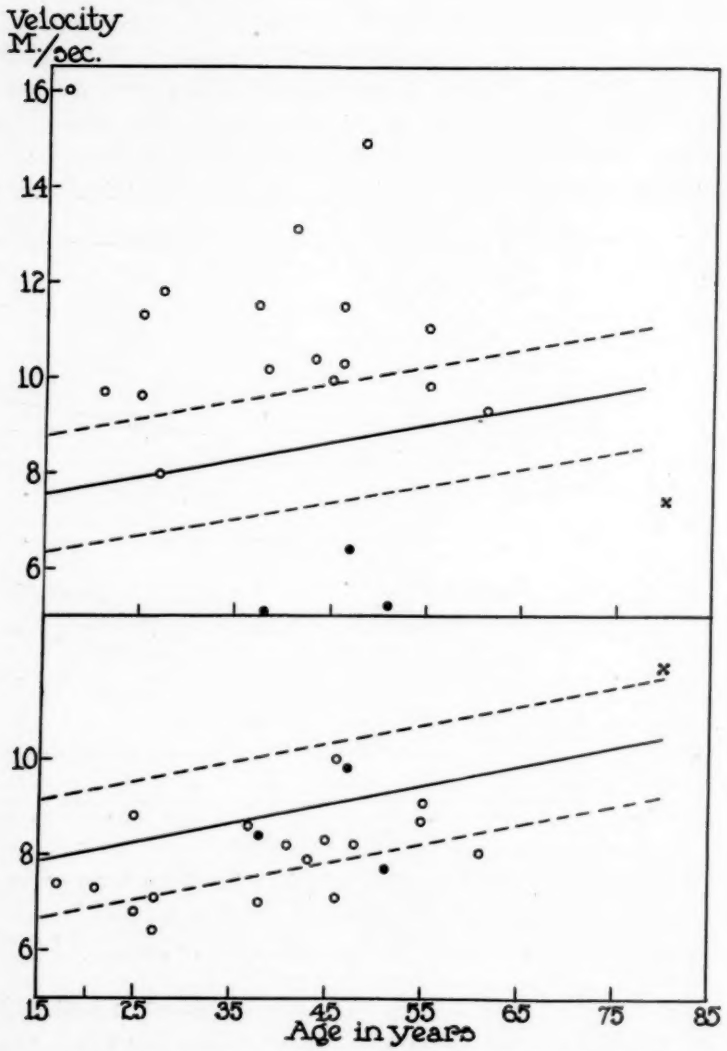

Fig. 10.—The velocities of the pulse wave in the brachioradial arteries of seventeen individuals with arterial hypertension (open circles) and of three with aortic insufficiency (closed circles) are shown according to age; above at natural diastolic pressures; below, calculated at 80 mm. Hg.

When one turns now to individuals with hypertension in whom the level of diastolic pressure is far different from normal, the effect of pressure on the velocity of the pulse wave becomes clear because it is great. The naturally recorded velocities in 18 patients in whom there was no

evidence of arteriosclerosis, were very high (from 8 to 16 M./sec.) (Fig. 10 upper). When their velocities are calculated at 80 mm. Hg they come to lie at, or even below, normal ones (Fig. 10 lower). Conversely, the velocities of normal arteries, calculated at 130 mm. Hg are as high as hypertensive ones. There is, then, no reason to believe that the distensibility of the larger arteries in patients suffering from hypertension differs from the normal except perhaps as an after effect of stretching, a phenomenon of considerable interest and one about which more will be said at another time. It can from these observations be inferred that the tone of their muscular coats is probably not greater than that of normal subjects. There are exhibited also three cases suffering from aortic insufficiency (closed circles Fig. 10) whose diastolic pressures ranged from 20 to 40 mm. Hg. They too have normal rates of transmission of the pulse wave at 80 mm. Hg.

COMMENT

If the speed of the arterial pulse wave is dependent upon the level of diastolic pressure, so far as it is dependent upon pressure at all, explanation of the close relation between speed of pulse wave and pulse pressure observed by Haynes, Ellis, and Weiss[4] becomes necessary. This relationship can be only indirect and the presence of other variables affecting both speed of the pulse wave and pulse pressure is, at once, suggested. In the several distinct groups of individuals from which the data were obtained—normal, hypertensive, arteriosclerotic, combinations of the two latter groups and a few individuals suffering from aortic insufficiency—certain factors which should affect both speed of pulse wave and pulse pressure would seem to be present.

First in hypertension the high diastolic pressure is the factor upon which both the high pulse pressures and high velocities of the pulse wave depend. For it has just been shown that speed of pulse wave increases with diastolic pressure. It is well-known that at high pressures a greater change in pressure is needed for the same change in volume than is necessary at low pressures.[18] Since there is considerable evidence that change in volume i.e., cardiac output and blood flow, is the same in hypertensive as in normal individuals[5, 19, 20, 21] the pulse pressure would, of necessity, be increased.

Secondly, in arteriosclerosis, the rigidity of the arterial wall is the factor upon which both the high pulse pressure and the high pulse wave velocity depend.

Thirdly, those individuals whose large pulse pressure is due to aortic insufficiency, and in whom there is no increase in rigidity of the arterial wall either from simple stretching (increase in diastolic pressure) or from changes in the constitution of the wall, exhibit a marked contrast to the two former groups. The large pulse pressure is not accompanied by a high velocity of the pulse wave. The velocities are, on the contrary,

rather low as are also the diastolic pressures. In short, velocity of propagation of the arterial pulse wave is not directly related to pulse pressure. Association of these phenomena is due to the presence of some third factor, in the present instances, marked stretching of, or change in structure of, the arterial wall upon which, on the one side pulse pressure, and on the other side velocity of the pulse wave, depends.

SUMMARY

1. It is well known that a considerable portion of the variation in arterial pulse wave velocity as measured in living individuals is due to size and thickness of wall, and to pressure within the walls, as well as to actual changes in elasticity of the wall itself. When an index of the elasticity of the arterial wall is sought by measuring pulse wave velocity, the error due to size and thickness of the wall can in part be taken into account only by measurements carried out upon the same artery; that due to pressure can be largely accounted for by individual relationships found to exist between speed of the pulse wave and pressure.

2. The pressure upon which the speed is dependent is not systolic, mean or pulse pressure but unequivocally diastolic pressure. The logical argument for this conclusion is supported by studies of pulse wave velocity carried out in dogs in which the levels of systolic and diastolic pressures were varied independently. The velocity of the pulse wave was not affected by variations in systolic pressure alone and hence neither by mean or pulse pressure. Changes in diastolic pressure only were regularly accompanied by changes in pulse wave velocity.

3. When the effect of the higher diastolic pressures occurring in hypertensive individuals without obvious arteriosclerosis is taken into account, it seems that the elastic properties and, inferentially, the tone of the muscular coats, of the larger arteries behave like those of normal ones.

ADDENDUM.—Since the above article was written, M. Prinzmetal and E. T. Oppenheimer have published observations upon patients with hypertension (Rôle of Arteries in Peripheral Resistance of Hypertension, Proc. Soc. Exper. Biol. & Med. **36**: 675, 1937) which strengthen the point of view just presented by furnishing evidence of an altogether different nature that arteries larger than the digital arteries are not necessarily involved in producing hypertension.

REFERENCES

1. Weiss, S., and Ellis, L. B.: The Quantitative Aspects and Dynamics of the Circulatory Mechanism in Arterial Hypertension, AM. HEART J. **5**: 448, 1930.
2. Prinzmetal, M., and Wilson, C.: The Nature of the Peripheral Resistance in Arterial Hypertension With Special Reference to the Vasomotor System, J. Clin. Investigation **15**: 63, 1936.
3. Pickering, G. W.: The Peripheral Resistance in Persistent Arterial Hypertension, Clin. Sc. **2**: 209, 1935-36.
4. Haynes, F. W., Ellis, L. B., and Weiss, S.: Pulse Wave Velocity and Arterial Elasticity in Arterial Hypertension, Arteriosclerosis and Related Conditions, AM. HEART J. **11**: 385, 1936.
5. Weiss, S., Haynes, F. W., and Shore, R.: The Relation of Arterial Pulse Pressure to the Hemodynamics of Arterial Hypertension, AM. HEART J. **11**: 402, 1936.
6. Moens, A. I.: Die Pulskurve, Leiden, Brill, 1878.

7. Hallock, P.: Arterial Elasticity in Man in Relation to Age as Evaluated by the Pulse Wave Velocity Method, Arch. Int. Med. **54**: 770, 1934.
8. Bramwell, J. C., and Hill, A. V.: The Velocity of the Pulse Wave in Man, Proc. Roy. Soc. ser. B. **93**: 298, 1922.
9. Wiggers, C. J.: Physiology in Health and Disease, Philadelphia, 1934, Lea and Febiger.
10. Frank, O.: Die Theorie der Pulswellen, Ztschr. f. Biol. **85**: 91, 1926.
11. Sands, J.: Studies in Pulse Wave Velocity. III. Pulse Wave Velocity in Pathological Conditions, Am. J. Physiol. **71**: 519, 1924.
12. Turner, R. H., and Herrmann, G. R.: Pulse Wave Velocity Under Varying Conditions in Normal and Abnormal Human Cardiovascular Systems, J. Clin. Investigation **4**: 430, 1927.
13. Bazett, H. C., and Dreyer, N. B.: Measurements of Pulse Wave Velocity, Am. J. Physiol. **63**: 94, 1922.
14. Eismayer, G., and Saeger, W.: Die Pulswellengeschwindigkeit in verschiedenen-Gefässgebieten; die Pulswellengeschwindigkeit in verschiedenen Gefässbieten bei Kreislaufgesunden im Ruhezustand und unter Einwirkung von Medikamenten, Ztschr. f. d. ges. exper. Med. **96**: 233, 1935.
15. Wezler, K.: Abhängigkeit der Arterienelastizität vom Alter und dem Zustand der Wandmuskulatur, Ztschr. f. Kreislaufforsch. **27**: 271, 1935.
16. Bramwell, J. C., McDowall, R. J. S., and McSwiney, B. A.: The Variation of Arterial Elasticity With Blood Pressure in Man, Proc. Roy. Soc. ser. B. **94**: 450, 1923.
17. Hemingway, A., McSwiney, B. A., and Allison, P. R.: The Extensibility of Human Arteries, Quart. J. Med. **21**: 489, 1928.
18. Fahr, G.: Work of the Left Ventricle in Normal Hypertension and Arteriosclerosis, Proc. Soc. Exper. Biol. & Med. **24**: 405, 1927.
19. Gladstone, S. A.: Cardiac Output and Arterial Hypertension. 1935. A partial report of the investigations conducted at Mt. Sinai Hospital, New York City.
20. Starr, I., Collins, L. H., and Wood, F. C.: Studies of the Basal Work and Output of the Heart in Clinical Conditions, J. Clin. Investigation **12**: 13, 1933.
21. Holman, D. V.: Cardiac Output in Essential Hypertension. Observations of the Effect of Sympathectomy. (To be published.)

Department of Clinical Reports

SIMULTANEOUS QUADRILATERAL ACUTE ULCERATIONS IN THROMBO-ANGIITIS OBLITERANS: REPORT OF A CASE*

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NEW YORK, N. Y.

IN THE years since von Winiwarter[1] first separated the syndrome which we now call thrombo-angiitis obliterans from the welter of ill-defined diseases of the circulation, physicians have learned to diagnose and treat the condition with increasing ease and accuracy. This report is deemed worthy of presentation because we have been unable to find any evidence, either by a search through the literature or by inquiry from the heads of a number of the largest vascular clinics in the country, of a previous patient with thrombo-angiitis obliterans who exhibited simultaneous acute quadrilateral ulcerations. The history and management of the patient also illustrate some specific problems in the diagnosis, treatment, and prognosis of the disease.

CASE REPORT

J. K., a thirty-nine-year-old American bus chauffeur of Aryan stock, was seen in the Vascular Clinic of the New York Post-Graduate Hospital on Feb. 23, 1937. He was admitted to the hospital on the same day.

His complaints dated back two and one-half years, when an ulcer developed on the tip of the right fourth finger. After several days of progression it was curetted down to the bone, and the wound healed slowly in a few weeks. Subsequently ulcers appeared on the third finger of the right hand, the fifth finger of the left hand, the second, third, and fourth toes and heel of the right foot, and the fourth toe of the left foot. A few had healed, but at the time of admission at least one lesion was present on each extremity, to be described below.

Treatment had previously consisted of diathermy, injections of unknown composition, and fever therapy in a hyperpyrexia apparatus, all without satisfactory response. About two months before admission, while in the midst of the hyperpyrexia treatment, a lesion which developed into an ulcer appeared on the left fourth toe, and with it severe rest pain occurred which was worse at night. Six weeks later cramp-like pains in the left calf were noticed, and at the time he was seen in the clinic the patient could barely walk because of this pain (whether this was true claudication or muscle strain, due to favoring the foot because of the open ulcer, could not be definitely determined).

There was no previous history of phlebitis, frostbite, or major illnesses or operations. He had smoked an average of 20 popular-brand cigarettes daily for years; ingestion of rye bread was rare. His weight had decreased 25 pounds in two years.

The general physical examination revealed no significant findings other than those noted below. Blood pressure averaged 106/78. The nails of all fingers were striated and brittle. The right fourth finger was about 0.5 cm. shorter than the corresponding finger on the left hand and the nail was curved down over the tip. This shortening had been produced by a previous ulcer, as above noted. All fingers showed chronic

*From the Vascular Clinic of the Department of Medicine, The New York Post-Graduate Medical School and Hospital of Columbia University.

rubor, especially the second and fifth on the left hand. There was a fluctuant discolored gangrenous area at the tip of the right third finger, and discoloration of the bed of the thumbnail. The left fifth finger was noticeably cooler than the other

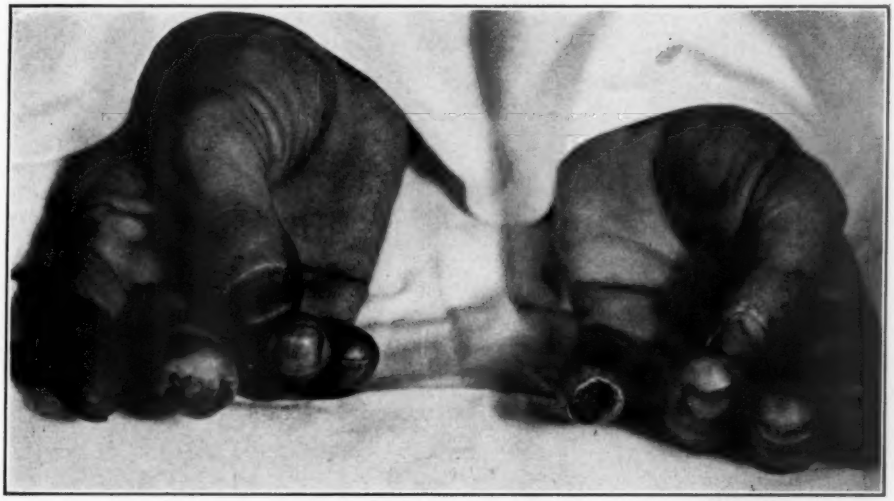

Fig. 1.—Appearance of hands on admission. Note ulcer on right third finger, down curving nail on right fourth finger, discolored nail bed of right first finger, ulcer on left fifth finger.

Fig. 2.—Appearance of feet on admission. Note ulcers of right third toe and left fourth toe. A large ulcer of the right heel does not show.

fingers, and at its tip was a black, sloughing and crusted ulcer from which pus in small amounts could be expressed. The Allen test[2] revealed defective filling of the left ulnar artery. The other major arteries of the upper extremities were smooth and strongly pulsatile (Fig. 1).

Fig. 3A.

Fig. 3, *A* and *B*.—Arteriograms of left and right hands. The digital arteries supplying the fifth finger of the left hand and practically all of the fingers of the right hand are not well visualized. The arteries proximal to the wrist are not involved.

The dorsum of the left foot was noticeably swollen. All toes showed rubor on dependence, especially the third and fifth on the right and the second and fifth on the left. On elevation all toes and the left foot blanched almost dead-white. On

Fig. 3*B*.

(See legend on opposite page.)

the medial aspect of the right third toe was a large irregular area of gangrene; on the heel was a shallow irregular ulcer 1.5 cm. in diameter. An irregular necrotic area was present on the dorsal aspect of the left fourth toe. Both feet were cool.

The major vessels of the lower extremities were strongly pulsatile except the right dorsalis pedis, which was feeble, and the left dorsalis pedis, which was absent. After edema had subsided there were times when this could be made out faintly (Fig. 2).

Oscillometric examination of the extremities yielded adequate readings at all levels except the feet, where small but definite deviations of the needle could be seen. Immersion of both upper extremities in water baths maintained at 42 to 46° C. (107.5 to 115° F.) for over forty minutes[3] failed to produce a rise in temperature in the toes, although there was a generalized vasodilatation. Tests with tobacco extracts for skin sensitivity, performed by Dr. F. H. Westcott of our clinic, were negative. Blood, serological, and urine examinations were negative. Blood cholesterol was 165 mg. per 100 c.c.

Arteriographic studies of the upper extremities with a contrast medium of thorium dioxide sol were performed, with the following findings (Fig. 3): in the right

Fig. 4.—Appearance of hands on discharge, seven weeks later.

upper extremity, the major vessels were well visualized down to the fingers. There was some degree of obliteration of practically all of the digital vessels, with occlusion most marked in the fourth finger. In addition there was trophic absorption of the terminal tuft of the ring finger, and similar, less marked changes in the middle and little fingers. In the left upper extremity all of the major vessels visualized well down to the fingers. There was obliteration of vessels supplying the fifth finger, and some obliteration of the arteries of the second and fourth fingers. Increased radiotransparency of the terminal phalanx of the fifth finger was observed. The changes as seen in Fig. 3 are typically those found in thrombo-angiitis obliterans. Unfortunately attempts at arteriographic studies of the lower extremities were unsuccessful.

Treatment.—Complete abstinence from tobacco was enforced. The patient was kept in bed, with the lower extremities continuously covered with a cradle and with a thermostatically controlled heating unit* which kept the temperature within the

*Cradle and thermostatically controlled heating unit furnished through the kindness of Valverde Laboratories, New York.

cradle at 33 to 35.5° C. (92 to 96° F.). The hands were immersed in warm boric acid baths for one hour three times daily for a week; at the end of this time the necrotic area at the tip of the left fifth finger could be lifted away, and the fluctuant tip of the right third finger had begun to drain pus. The nails were kept trimmed and small crusts were removed daily. After the first week the hands were soaked twice daily, and finally once daily. For the first few weeks the fingers were bandaged in dry dressings between soaks; thereafter no dressings were used.

The ulcers of the toes and heel were covered with wet dressings of azochloramid in triacetin solution, 1:500. These were kept wet continuously during the day. The skin of both lower extremities was kept soft with lanolin.

In addition to these local measures the patient was given typhoid vaccine* intravenously, beginning with a dose of five million bacilli and increasing each dose

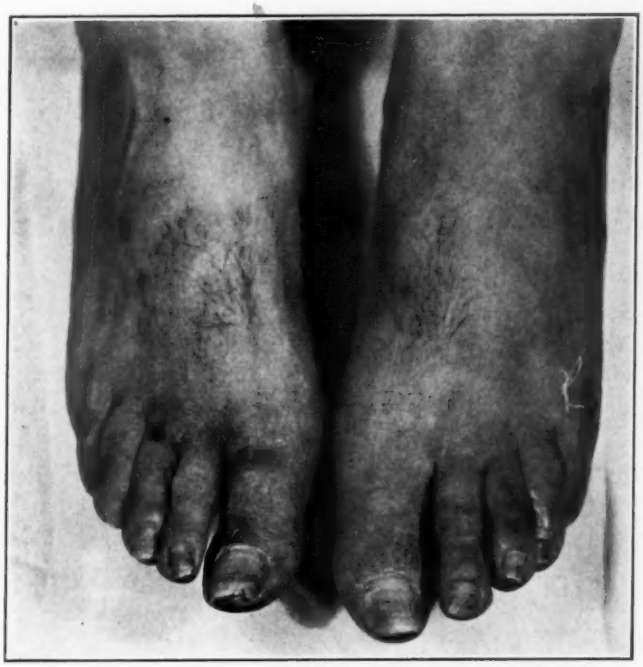

Fig. 5.—Appearance of feet on discharge, seven weeks later.

by five or ten million organisms, depending upon the height of the fever reached with the preceding injection, the object being to obtain about two degrees C. of fever without chill. He received three injections weekly for the first four weeks, and two injections weekly thereafter.

Within a week the ulcer of the right third toe healed, and a few days later the heel covered over. The ulcer of the left fourth toe responded more slowly, but by the end of the second week the purulent discharge had ceased and a dry scab formed, which was slowly lifted off, revealing smooth new epithelium beneath.

The patient was discharged on April 14, 1937, seven weeks after admission. The condition of the extremities at this time is shown in Figs. 4 and 5. All ulcers had healed. The nail of the right third finger had fallen off. This finger continued

*Typhoid vaccine, 100 million organisms per cubic centimeter. Prepared for intravenous use and supplied through the courtesy of the C. F. Kirk Company, Bloomfield, N. J.

to be cyanosed. A small scab covering the depressed area was the only evidence of the large necrotic ulcer at the tip of the left fifth finger. Five weeks after discharge he was back at work, free from symptoms and without recurrence of open lesions.

COMMENT

Thrombo-angiitis obliterans most frequently first attacks the vessels of the feet, but it may appear in the upper extremities alone or in combination with the lower extremities. The disease is, moreover, characteristically remissive and migratory, and open lesions do not usually appear on more than one or two extremities simultaneously. This is the first case in our experience, and in the experience of several large vascular clinics in this country, presenting the typical painful ulcers of the disease on all four extremities at the same time. It is of particular interest also because in spite of the widespread involvement the lesions as determined by arteriographic and oscillometric studies were practically confined to the smaller terminal portions of the vascular tree. Buerger[4] has described a few cases in which there was symptomatic involvement of both upper and both lower limbs and ulcerations in two or three, during the protracted course of the disease. In 1932, Ito and Asami,[5] reporting 27 patients treated by lumbar and sacral ganglionectomy, mention one in whom ulcers appeared serially on the digits of all four extremities over a period of years. This was not uncommon, of course, when the disease was allowed to progress unchecked before the present-day therapy was understood. Starr[6] describes a man who had successive involvement of hands and feet, and who at one time had ulcers on the acral portions of three limbs.

Treatment was completely conservative. As has been definitely demonstrated,[7] abstinence from tobacco is the primary, cardinal principle in the treatment of this disease. We have found azochloramid in triacetin, 1:500, to be a helpful antiseptic wet dressing for use in purulent ulcers of the type described. Fever up to 39° C. (102° F.), without rigor and its accompanying marked vasoconstriction, was attained by the intravenous use of the dilute typhoid vaccine above noted. The height of this nonspecific type of fever was regulated by increasing the dose by five or ten million bacilli with each injection if the preceding treatment had not produced a chill or too severe a febrile reaction. There was relief of the intense pain in the ulcerated areas after the second injection; this is a frequent experience with typhoid vaccine. The use of thermostatically controlled heat as recommended by Starr[8] is extremely important, since overheating of the extremity increases metabolic demands, with resultant increase of pain and spread of gangrene. The temperature should be kept between 33 and 35.5° C. (92 and 96° F.).

Although the ulcers were completely healed at the time of discharge and have remained so to date, and although the patient no longer has claudication or rest pain, there is grave danger of a recurrence following either smoking or local trauma to the extremities. We can

state, moreover, which fingers are in the most precarious condition, as follows: in the right hand the third and fourth fingers especially, and in the left hand the second, fourth, and fifth fingers. These conclusions are based on the arteriographic studies which show the most marked deficiency in the arterial circulation to be present in the fingers mentioned. In other patients it has been possible to predict where the next lesions would occur, in the event of smoking or trauma, with a high degree of accuracy.

SUMMARY

The case history of a patient suffering from thrombo-angiitis obliterans with acute simultaneous quadrilateral gangrenous lesions is presented. A search of the literature and inquiry among a number of the major vascular clinics in the United States has failed to reveal a record of any preceding example of this disease with quadrilateral simultaneous lesions.

An outline of what we consider to be the most satisfactory form of therapy for thrombo-angiitis obliterans is included. After considerable experience we have not been impressed with the results from new forms of mechanical apparatus, despite the broad claims which have been made for them.

REFERENCES

1. Von Winiwarter, Felix: Über sine eigenthümliche Form von Endarteriitis und Endophlebitis mit Gangrän des Fusses, Arch. f. klin. Chir. **23**: 202, 1879.
2. Allen, E. V.: Thrombo-Angiitis Obliterans: Methods of Diagnosis of Chronic Occlusive Arterial Lesions Distal to the Wrist, With Illustrative Cases, Am. J. M. Sc. **178**: 237, 1929.
3. a. Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in the Lower Extremities in Response to Immersing the Forearm in Warm Water, J. Clin. Invest. **11**: 1019, 1932.
   b. Landis, E. M., and Gibbon, J. H., Jr.: A Simple Method of Producing Vasodilatation in the Lower Extremities, Arch. Int. Med. **52**: 785, 1933.
4. Buerger, Leo: The Circulatory Disturbances of the Extremities, Philadelphia, 1924, W. B. Saunders Company, Chapter LIX.
5. Ito, H., and Asami, G.: Lumbosacral Sympathetic Ganglionectomy: Its Value as a Therapeutic Measure for Thrombo-Angiitis Obliterans, Am. J. Surg. **15**: 26, 1932.
6. Starr, Isaac: Carbaminoylcholine-(Doryl or Lentin). Its Action on Normal Persons, in Peripheral Vascular Disease, and in Certain Other Clinical Conditions, Am. J. M. Sc. **193**: 393, 1937.
7. a. Maddock, W. G., and Coller, F. A.: Peripheral Vasoconstriction by Tobacco Demonstrated by Skin Temperature Changes, Proc. Soc. Exper. Biol. & Med. **29**: 487, 1932.
   b. Barker, N. W.: Vasoconstrictor Effects of Tobacco Smoking, Proc. Staff Meet. Mayo Clin. **8**: 284, 1933.
   c. Maddock, W. G., and Coller, E. A.: Peripheral Vasoconstriction by Tobacco and Its Relation to Thrombo-Angiitis Obliterans, Ann. Surg. **98**: 70, 1933.
   d. Wright, I. S., and Moffat, Dean: The Effects of Tobacco on the Peripheral Vascular System, J. A. M. A. **103**: 318, 1934.
   e. Silbert, Samuel: Thrombo-Angiitis Obliterans (Buerger). IX. Surgery, Gynecology, and Obstetrics **61**: 214, 1935.
   f. Lampson, R. S.: A Quantitative Study of the Vasoconstriction Induced by Smoking, J. A. M. A. **104**: 1963, 1935.
8. a. Starr, Isaac, Jr.: A Thermoregulated Foot Cradle for the Treatment of Peripheral Vascular Disease, Proc. Soc. Exper. Biol. & Med. **29**: 166, 1931.
   b. Starr, Isaac, Jr.: On the Conservative Treatment of Gangrene of the Feet by a Selected Temperature, Oxygen and Dessication, Tr. A. Am. Physicians **47**: 339, 1932.

Society Transactions

AMERICAN HEART ASSOCIATION, 1937

The thirteenth annual scientific session of the American Heart Association was held on June 7 and 8, 1937, at Hotel Haddon Hall, Atlantic City, N. J.

Dr. E. M. Landis, of Philadelphia, presided at the meeting of the Section for the Study of the Peripheral Circulation on Monday, June 7. The following program was presented.

PROGRAM OF THE SECTION FOR THE STUDY OF THE CIRCULATION

Observations on Phlebitis. Edward A. Edwards, M.D., Boston, Mass. See page 428.

The Treatment of Scleroderma by Means of Acetyl Beta Methyl Choline Chloride (Mecholyl) Iontophoresis. A. Wilbur Duryee, M.D., and Irving S. Wright, M.D., New York, N. Y. To be published.

The Pathological Basis for Intermittent Claudication in Arteriosclerosis. J. Ross Veal, M.D., New Orleans, La. See page 442.

Studies in the Pathology of Vascular Disease. Milton C. Winternitz, M.D., R. M. Thomas, M.D., and P. M. Le Compte, M.D., New Haven, Conn. See page 399.

Experiences With the Conservative Management of Sudden Occlusion of Arteries of the Extremities. Louis G. Herrmann, M.D., Cincinnati, Ohio.

ABSTRACT

The important factors in the symptomatology and diagnosis of acute arterial occlusion are emphasized and the mechanism of production of the acute arterial insufficiency after embolism, thrombosis and ligation is discussed. Special emphasis is placed upon vasoconstriction and segmental arterial spasm which is usually present. Vasodilatation must be brought about early to prevent disintegration of tissue while an adequate collateral arterial circulation is being established. The mechanism of the establishment of collateral arterial circulation and the ways of aiding its establishment by drug therapy, controlled environmental temperature, light superficial massage, optimum level of resting extremity, and passive vascular exercises are discussed. The physiological basis for the use of passive vascular exercises is presented with emphasis upon the type of alteration of the environmental pressures most suited to do this work. The danger of excessive heat, elevation, or persistent venous congestion is emphasized, and the four main courses which any acute arterial occlusion may take are shown.

Our experience with twenty-one instances of acute major arterial embolism, twenty-five instances of acute major arterial thrombosis, and nine instances of acute arterial occlusion due to trauma or ligation is presented. In summarizing the results of conservative therapy, only six major amputations were performed in fifty-

three cases. At the end of three months, forty-one patients were living and well. On the basis of our experiences during the past five years, we believe the conservative measures are indicated in most cases of acute arterial occlusion.

Factors Affecting Vascular Tone (George Brown Memorial Lecture). Walter B. Cannon, M.D., Boston, Mass. See page 383.

Hypertension Produced by Constriction of the Renal Artery in Sympathectomized Dogs. Norman E. Freeman, M.D., Philadelphia, Pa., and Irvine H. Page, M.D., New York, N. Y. See page 405.

Interpretation of Arterial Elasticity From Measurements of Pulse Wave Velocities. J. Murray Steele, M.D., New York, N. Y. See page 452.

The Physiological Effects of Extensive Sympathectomy for Essential Hypertension. Edgar V. Allen, M.D., and A. W. Adson, M.D., Rochester, Minn. See page 415.

Discussion

Discussion of the paper, "Observations on Phlebitis," by Dr. Edwards.

Dr. Alton Ochsner, New Orleans, La.—As probably many of you know, Bancroft and his associates for a number of years have attempted, in postoperative cases, to differentiate the potential clotters from potential bleeders; and in a recent communication before the American Surgical Association last week they reported a relatively large series of cases and found that in the cases examined postoperatively approximately 12 per cent were potential clotters. It was in this group of individuals that they believed they could accomplish a great deal prophylactically by giving the patients sodium thiosulphate and also by putting them on a low protein and high carbohydrate diet.

As regards the therapeusis of thrombophlebitis, for approximately five years we have been using leeches. We have revived probably one of the oldest therapies in medicine, and the results have been gratifying. We have had a few more than fifty cases, and it is quite remarkable what can be accomplished if, as soon as the phlebitis occurs—and the sooner the therapy is instituted the better the results—one will apply leeches along the course of the vein. If from four to eight leeches are applied, the number depending upon the severity of the case, usually within five to six hours the pain is completely relieved; within twenty-four hours the temperature has begun to fall, and the convalescence is shortened by weeks.

At the time we made our report three years ago, the suggestion was made that leeches might be used in the treatment of thrombosis of the coronaries. Dr. Lilienthal, of New York, tells me that he has observed two such cases in which leeches were used. Hirudin, which is an active principle of the leech's head, will cause a softening and will dissolve a clot in vitro, which can be demonstrated very readily. The systemic effect of the hirudin is marked as well as the local effect.

Relatively recently in Toronto heparin has been used postoperatively. Dr. Galli informs me that he and his associates, in approximately 300 cases, have used intravenous infusions of heparin postoperatively and have eliminated the incidence of postoperative thrombosis and embolism.

The advantage of Bancroft's work is that one is able to detect these potential clotters. Dr. Lilienthal is so convinced of the efficacy of leeches that he now uses four leeches in every laparotomy. He applies the leeches on the fifth day, and, although his experience has not been large since the institution of this therapy, he believes that he can eliminate thrombosis and embolism.

Dr. N. W. Barker, Rochester, Minn.—I was very much interested in Dr. Edwards' excellent paper. He has brought out several points which stimulate further investigation of the somewhat neglected problem of thrombophlebitis.

It is a rather unfortunate commentary on our medical progress that we have discovered very little concerning the etiology of thrombosis and thrombophlebitis since Welch wrote his classical article on the subject in 1898. Welch stated that there were probably three factors concerned in the production of intravascular thrombosis: a local lesion of the vessel which might be degenerative, infectious, or toxic in origin; a disturbance of the clotting mechanism of the blood; and stasis of the blood stream.

Experimental evidence is still conflicting regarding the rôle of direct bacterial injury to the intima of the vein as the starting point for the thrombophlebitis which follows operation, childbirth and severe infectious disease, for it is usually impossible to recover the organisms from the lesion in the vein itself. However, we almost always consider that the lesion of the intima may be caused by a toxin elaborated from bacteria in some distant part of the body.

I would like to ask Dr. Edwards if the evidence of sympathetic stimulation and irritation in femoral and iliac thrombophlebitis has been observed consistently or is an exceptional occurrence.

I disagree with him regarding the harmlessness of the injection of varicose veins in which spontaneous acute or subacute thrombophlebitis exists. I have seen one such case in which a marked extension of the thrombosis into the femoral and iliac veins followed injection of a varix in which there was localized subacute spontaneous thrombophlebitis. Also, I have seen a similar case in which injection was followed by extensive cellulitis of the leg and septicemia.

When one is confronted with a case of thrombophlebitis, particularly if it occur following an operation, one always considers the possibility of a pulmonary embolism. However, the evidence is accumulating that once the clinical signs of thrombophlebitis of the large veins of the leg are definitely manifest, the danger of the thrombus becoming an embolus is very small, approximately 2 per cent in a series which I have recently studied. Conversely, in a fairly large number of cases of fatal pulmonary embolism, in only 4 per cent had there been previously recognizable femoral or iliac thrombophlebitis. When one makes a histological examination of the actual embolus which produces death in these cases, organization at the margins of the embolus is absent. We know that organization of a thrombus in a vein takes place rapidly. Therefore, it would seem that these emboli are detached portions of a relatively fresh thrombus which may have been present only for a matter of minutes or hours. Once the signs and symptoms of clinical thrombophlebitis are present, it is probable that the patient is pretty well protected against the loosening of that particular clot. I have seen only five cases in which fatal pulmonary embolism followed a femoral or iliac thrombophlebitis. In each instance necropsy proved that the embolism did not come from the limb where the phlebitis was recognized clinically but from the opposite limb which previously had not exhibited signs of thrombophlebitis. Therefore, the danger of pulmonary embolism in cases of clinically recognizable thrombophlebitis of the femoral and iliac veins lies in the possibility of the development of an entirely fresh thrombus in a different vein due to the persistence of the same factors which were responsible for the original thrombophlebitis. I believe that this is an important point to be considered in the treatment of these cases.

Dr. Edwards.—Dr. Barker has raised the question of the frequency of the phenomena due to sympathetic irritation. Some of the less startling reactions, such as the sweating, are fairly common. Minor degrees of arteriolar constriction giving

coldness are also common. Constriction of the larger arteries as evidenced by coldness and diminution in the arterial pulse is less frequently seen but is not rare. Finally, complete spasm of a major artery, such as a femoral, is rare.

In the treatment of varicose phlebitis, I believe the ligation to be most important. The injections are less important and can sometimes be omitted. I quite agree that using large doses of sclerosing fluid may temporarily increase the *inflammation*, but I have never seen bacteriological evidence of *infection* result. The fluid should be injected in small amounts, and in only one or two areas at one sitting.

Discussion of the paper, "The Treatment of Scleroderma by Means of Acetyl Beta Methyl Choline Chloride (Mecholyl) Iontophoresis," by Dr. Duryee and Dr. Wright.

Dr. Edgar V. Allen, Rochester, Minn.—I wish to compliment Dr. Duryee and Dr. Wright on this contribution. While I have had no actual experience with this method of treatment, I have observed some of the cases treated by Dr. Duryee and Dr. Wright, and it did seem that these patients were improved.

It is to be hoped that the essayists will use some objective method of measuring improvement, but the fact that they have not done so does not discount in any way the results which they have reported.

It has been said that the diminution in circulation in scleroderma is a direct result of the tightening of the skin which interferes with the flow of the blood through the arteries and arterioles. However, arteriography offers evidence that this is not true, for the arteriograms in scleroderma have much the same appearance as do those in uncomplicated Raynaud's disease in which there is no tightening of the skin to interfere with the circulation. Two common findings in both acrosclerosis and uncomplicated Raynaud's disease are absence of the filling of the distal portions of the digital arteries and diminished caliber of these arteries. It appears, therefore, the mechanism of the diminution of the peripheral circulation is the same in Raynaud's disease and acrosclerosis. There is also clinical evidence for this, as many patients with acrosclerosis have vasomotor symptoms indistinguishable from Raynaud's disease, and many patients with uncomplicated Raynaud's disease may develop scleroderma subsequently as a complication of that condition.

At the Mayo Clinic we have had considerable experience with ganglionectomy in the treatment of scleroderma. The results are from good to indifferent, and so many of them are indifferent or poor that one welcomes an additional method of treatment of this very disturbing condition.

I was particularly impressed by the observation pointed out by the essayists that scleroderma improves not only in the areas to which iontophoresis is applied but in other areas as well. This would imply that the improvement is not due to local action but to some general effect.

I should like to ask Dr. Duryee and Dr. Wright if they have tried application of mecholyl by inunction. I should like to ask also if Dr. Duryee and Dr. Wright consider the possibility of the development of sclerosis of the coronary arteries in their patients. It has been shown that repeated infusion of mecholyl into dogs leads to a high degree of sclerosis of the coronary arteries.

Finally, I should like to say that this is a very excellent contribution, and it has been extremely pleasant to hear the subject presented so conservatively and to hear encouragement about this type of treatment.

Dr. Wright.—I will not attempt to answer Dr. Allen's question because Dr. Duryee can do that quite ably. Since Dr. Duryee left New York several days ago, however, I have seen the first patient who I believe has had a more or less serious

relapse following this therapy, and this serious relapse brings up the question as to the mechanism by which this disease is caused, because this woman has been subjected to a very great nervous shock. As we go over our patients with scleroderma, I think we are all impressed with the fact that a considerable percentage of these individuals have been subjected to some rather serious nervous strain preceding the onset of the illness, but even more often, it happens that in the course of the disease they are made suddenly much worse by nervous shocks. This woman had a daughter in a very severe automobile accident, and being assured that plastic surgery would produce a good result as far as the facial deformity went, submitted her to an operation. Instead of success, she discovered within the last few weeks that it is doomed to failure because of infection, and the girl will have many more scars on her face than she had to begin with. This girl being in her early twenties, the mother has taken it very seriously, and the results have been, as I say, the first really serious relapse we have seen during this form of therapy.

From an etiological angle, I think we must conclude, on the basis of this and our other experiences, that central nervous mechanisms, or sympathetic nervous mechanisms, probably play a greater part in the production of this type of phenomenon than local change in the subcutaneous or cutaneous tissues.

Dr. Geza de Takats, Chicago, Ill.—We have struggled with the problem of scleroderma, and welcome the suggestion of Dr. Duryee and Dr. Wright that we treat these patients with iontophoresis.

I have tried ganglionectomies with no avail. I have done one parathyroidectomy with negligible results. Our observations on iontophoresis are limited to two cases, but I want to bring out one point as objective evidence of improvement, and that is the measurement of the resistance of the skin to the galvanic current, which can be expressed in ohms and for which measurement some of the more recent instruments are equipped. The last case, which showed a very marked improvement, showed that the galvanic skin resistance dropped from 40,000 ohms to 4,000, which I believe is very definite evidence that there is less thickening of the skin.

The skin contains much more calcium in the affected than in the control regions, but nevertheless we have never regarded these sclerodermic areas as caused primarily by a disturbance of calcium metabolism. I feel that the process is of a chronic inflammatory nature, that calcium is simply deposited there, and it is possible that changes in the parathyroids are just a secondary reaction to the local deposits of calcium.

Dr. William A. Sodeman, New Orleans, La.—I think it of interest to report on a patient of Dr. Ochsner's on whom Dr. Burch and I measured the tissue pressure by a direct objective method for determining the pressure in skin and subcutaneous tissues. This patient had had a right cervical sympathectomy and a parathyroidectomy so that we had control on one side of the effect of the parathyroidectomy alone. The tissue tension in this patient was the highest we have ever taken, 338 mm. of water. Two weeks following the operation the patient had marked subjective improvement and objective improvement as well, as far as movement of the extremities and so on is concerned, and the tissue pressure had dropped about 125 mm. of water. The tissue pressure was the same on both sides, indicating that the result was due to the parathyroidectomy and not to the sympathectomy.

Dr. Duryee.—In answering Dr. Allen's question as to the use of mecholyl by inunction, I should like to state that we have used it in this manner but not with this group of patients. We have been trying for the last three or four years to develop a simpler slow method of absorption from the skin, but so far our results

have been discouraging. In the future we should control some of these patients by treating them with mecholyl over the unaffected areas to see if we get the same improvement.

The question of coronary sclerosis is important in view of the fact that we have had three deaths in this series. However, in none of the three cases was there any definite evidence that the death was due to coronary disease. One patient died of bronchopneumonia. The other two had electrocardiograms during their time in the hospital, and these electrocardiograms were normal; unfortunately in neither case was there an autopsy.

I am much interested in the work of measuring tissue tension. Dr. de Takats' suggestion of measuring skin resistance adds another objective test for improvement. There is a lot more work to be done in this field before we can really evaluate this form of treatment.

I wish to thank the discussers for their opinions and for their added discussions.

Discussion of the paper, "The Pathological Basis for Intermittent Claudication in Arteriosclerosis," by Dr. J. Ross Veal, New Orleans, La.

Dr. Benjamin Jablons, New York, N. Y.—We have studied this problem from a different angle, and our results go far to confirm the results which Dr. Veal has presented this morning.

By means of a method which we have termed electromyography, we have applied the principles underlying electrocardiography to a study of muscle function in normal and in diseased individuals, and we have found that normally we get a type of muscle curve which is associated with apparently normal circulation in the muscle.

However, when this circulation is interfered with either artificially or as a result of disease processes, a change in this type of curve occurs, and we have found that by compression, even to a degree where complete obliteration or complete obstruction of the vessel does not occur, a change in the muscle curve is produced; instead of having the normal, monophasic curve, we get a diphasic curve which is always present, even when the compression has not gone to the point of completely obliterating the circulation through the major trunks.

We have found this method of great value in making a diagnosis in early cases of peripheral vascular disease in which there is no obliteration of pulse, in which the oscillometer fails to give you sufficient information to suggest that there is vascular disease, but in which symptoms are present of the nature of intermittent claudication.

Dr. A. W. Oughterson, New Haven, Conn.—I am sure we have all been interested in the observations which Dr. Veal has made of the occasional failure of correlation between the degree of obstruction and the presence of claudication, and I would like briefly to call attention to one method of producing claudication, which we perhaps all recognize, namely, the vasomotor spasm.

It is now well recognized that many diseases with vasomotor spasm may result in claudication, but I doubt if it is very widely recognized that in arteriosclerosis also, at least in the early stages, vasomotor spasm may play an important rôle. The incident which first called this to my attention was the temperature studies in an individual with an obstructive, vascular lesion, in which the temperature of the involved limb at rest was higher than that of the normal limb at a room temperature of 68 degrees. However, following exercise the temperatures of the limbs were reversed, the normal limb showed a vasodilatation and the involved limb a vasoconstriction. This would seem to indicate that in the early phases of obstruction, and obstruction which may be due to arteriosclerosis, the vasomotor spasm may explain some of these cases of intermittent claudication, which it is difficult to

explain otherwise. This vasospasm may be manifest only during exercise, and studies carried out on the limb at rest may actually show an increased blood flow in the limb with an obstructive lesion.

Dr. Veal.—I would like to thank these gentlemen for their discussion of my paper. There is one point I would add that we have not included in this paper. We have made a series of oxygen saturation studies on these patients and compared these oxygen changes with those found in the normal patient before and after exercise. The oxygen saturation changes are similar in both groups of patients. There was no greater decrease in the oxygen saturation of the venous blood of the claudication cases during their exercise pain than in the normal patients under a similar amount of exercise.

Discussion of the paper, "Studies in the Pathology of Vascular Diseases," by Dr. Winternitz, Dr. Thomas and Dr. LeCompte.

Dr. Emanuel Libman, New York, N. Y.—I do not think that it would be proper to let this paper go without discussion. It seems evident that Dr. Winternitz and his associates have opened up an entirely new chapter in the whole subject of the pathology of the blood vessels.

Incidentally, this work makes clearer our conception of the way of development of mycotic embolic aneurysms. It shows that they may originate in infection by way of the lumen as well as by the proved pathway of embolic infection of vasa vasorum.

In the course of the presentation, Dr. Winternitz made very clear the essential differences between the pathology of Buerger's disease and arteriosclerosis. I emphasize this point because papers have appeared in which the lesions of Buerger's disease are classed as arteriosclerosis.

This work may well prove important in also throwing light on the changes in the vessels in cases of acute arteritis. I have no doubt that Dr. Winternitz has thought about that and has ideas on the subject.

Dr. Winternitz.—I have nothing to add except to thank Dr. Libman, of course, and to say that I think all aneurysms should be considered anew in the light of the function of the different coats of the blood vessel.

For instance, there can be no doubt that the dissecting aneurysm arises from hemorrhage within the vessel wall; it does not have its origin from a tear of the innermost surface. Mycotic aneurysms may result from embolic processes in the vasa of the vessel wall. One sees evidences of this possibility in the extension of the inflammatory processes to the artery wall from the surrounding tissue. The rate of progression of the process in the surrounding tissue results in many different vascular changes, many of which are exemplified in the tuberculous lung. The rapid occlusions are thrombotic in character; otherwise the vessel would not be obliterated and extensive hemorrhage would be more frequent.

It may be permissible to make one other point. Vessels arising from the intima and dividing into capillaries in the vessel wall, i.e., the intima, have their analogy in the heart valves. Such vasa of the vessel wall may be the portals for mycotic infection leading to aneurysm, and it is conceivable that the vessel arising from the surface of the heart valves may play a similar part in endocarditis.

Discussion of the paper, "Experiences With the Conservative Management of Acute Arterial Occlusion," by Dr. Herrmann.

Dr. Geza de Takats, Chicago, Ill.—In analyzing Dr. Herrmann's results, one is impressed by the high percentage of recovery of both limb and life. In fact, in looking over the available literature, the most important of which is the collective

review of the Scandinavian surgeons as shown by Nystrom, it is perfectly obvious that Dr. Herrmann's results are far superior to any results published in the world literature.

You may remember that in the Scandinavian statistics, 60 per cent of a total 382 patients died; 20 per cent required amputation; and only 20 per cent left the hospital with a restored circulation; one-half of these patients were dead in three years.

Now, obviously, the factors that determine the ultimate outcome of a limb affected by a vascular occlusion can be readily grouped into those which are out of our control and those which we can control. We cannot control the condition of the heart, although I will come back to that point in a minute. We cannot control the condition of the vessel wall at which site the thrombosis occurs. We may control the time element, and we can control, as Dr. Herrmann has emphasized, the state of the collateral vascular bed.

In regard to the condition of the heart, under the influence of Dr. Gilbert and Dr. Fenn, who are particularly interested in coronary circulation, I have been impressed with the damage done by digitalization of these patients. Such patients, when an acute embolus occurs, are in a state of shock. It is the consensus of opinion of the medical men working with us in Chicago that a great number of emboli occur because of a sudden overdigitalization of these patients, particularly if the emboli are secondary to coronary occlusion.

I have no opinion to offer on the subject, but just bring this to your attention, because in the last five cases of embolism that I have seen, all of which were multiple, by the time we got to see the patient, the patient had already received massive doses of digitalis although there was no obvious cardiac decompensation.

With regard to the time element, I believe that papers like Dr. Herrmann's, and his teachings, writings, and his active work all around the country will finally give us the opportunity to see these patients earlier. We are not as fortunate in Chicago. I notice that half of his patients had arrived at the hospital (or perhaps they may have been at the hospital) before twelve hours had elapsed. In our material, most of the patients arrive so late that all we can do is to amputate, and I believe that the emphasis on the utmost urgency of seeing these patients early and instituting adequate, conservative treatment will save many lives and many limbs.

The peripheral vasodilatation, as Dr. Herrmann has said, can be accomplished by a moderate amount of heat, by drug therapy, by vascular exercise, and by observing the optimum level of circulatory efficiency. Recently, we have used small doses of sodium nitrite because it acts faster than papaverine and because later on it can be followed by injections of papaverine.

It should be remembered that no drug should be used that will lower general blood pressure to any extent because if it does, it will increase peripheral stagnation in the venocapillary bed.

From all this it would seem, then, that embolectomy is an obsolete procedure. Dr. Herrmann has avoided mentioning under what conditions he would now perform embolectomy, and I feel very strongly, and agree with him, that embolectomy is not indicated, first of all in thromboses; second, it is not indicated if conservative measures succeed, such as he has described, and finally it is not indicated after ten to twelve hours, although there are a number of patients reported, particularly by Dr. Pearse, who have had their circulation restored after twelve hours.

Now the question comes up, should embolectomy be done at all? In my own material, which now comprises fifteen cases of embolism and thirty-five cases of thrombosis, there are only three patients in whom I felt embolectomy should be

done. These were the patients who were seen within ten or twelve hours, and who had shown no definite improvement after conservative measures. I feel that in such cases, with a small exposure under local anesthesia, with adequate equipment, and with adequate, trained assistants, we can do no harm and we may restore circulation.

The only reason I believe embolectomy should not be discarded entirely is that the limb from which an embolus has been removed shows a far better circulation than the limb which has been saved by conservative measures. Dr. Herrmann has dwelt on this in detail. He has said that very often these patients have an ischemic neuritis, muscle atrophy, bone atrophy. These limbs are sometimes so painful and so useless that they have to be amputated, and, when there is a chance of restoring the circulation so the pulse actually becomes palpable and the major arterial pathways are restored, this benefit should be given to the patient.

But I thoroughly agree with him that embolectomy is a complicated, delicate procedure, and in the hands of the casual surgeon can do more harm than good.

In regard to amputations, I feel that, when the patient has been seen twelve, twenty-four or forty-eight hours after the attack, amputations should be urged, because I have in my material some patients who have survived multiple emboli, even though one or two of these emboli have occurred in the brain, and who are now fairly useful members of their community. The attitude still prevails among the general practitioners, among the internists, and also among the surgeons that once the patient has had an embolus and gangrene is present, it is just as well to let that patient die. That is a very faulty view, particularly when you know of some patients who have not only been relieved from their incessant pain and from the danger of sepsis, but whose lives were saved.

I wish to say that I had the opportunity of reading Dr. Herrmann's paper in full, and I am greatly impressed by the excellent results shown by him. They are partly due to his education of the medical profession around Cincinnati, which enabled him to see these patients in a large percentage of cases within twelve hours.

Dr. Norman E. Freeman, Philadelphia, Pa.—I am sure that we are all grateful to Dr. Herrmann for the clear presentation of his experiences in the treatment of acute arterial occlusion.

One additional mechanism may be worth considering, and that is the reflex vasoconstriction which occurs after the development of thrombosis or embolism. Constriction of the collateral vessels may determine whether or not the patient will lose his limb or even his life. We do not know whether the vasoconstriction takes place as a local reflex from local trauma to the vessel at the site of the obstruction or whether it takes place as part of the generalized reflex vasoconstriction which is the body's response to any traumatic stimulus. Recent observations on experimental animals have indicated that reflex constriction does occur in collateral vessels. Pharmacological vasodilatation by the use of drugs has been discussed. I should like to stress the importance of the prevention of physiological vasoconstriction. Since it is recognized that traumatic stimuli such as pain, cold, fear, and reduced blood volume produce contraction of the blood vessels throughout the body, control of these factors is necessary in order to assure adequate blood supply to all the tissues of the body. Only in case the general condition of the patient can be brought to its optimum position can the blood flow throughout the entire body be maintained at an adequate level.

I think that it is particularly significant that such a surgical authority as Dr. Herrmann should tell us not to use surgery.

Dr. H. Vesell, New York, N. Y.—I would like to ask Dr. Herrmann whether he has any determinations on the blood pressure after the administration of papaverine.

Dr. J. A. Oille, Toronto, Ont.—I would like to congratulate the surgeon on an excellent medical paper. It is quite an extraordinary experience. I would also like to ask Dr. Herrmann when he would do an embolectomy.

Dr. Herrmann.—For lack of time I have had to omit the discussion of many important points. The point that Dr. Freeman brought up, the general treatment of the patient, is most important and should have been emphasized. Dr. Landis and Dr. Freeman have shown that reflex vasodilatation is an important factor to be considered in this therapy.

The question of when to do an embolectomy and when not to is one which I cannot answer in so many words. I entirely agree with Dr. de Takats when he says that it should be done in a limited number of patients because, when possible, it is the best way of reestablishing circulation. The thing that I am trying to discourage is embolectomy attempted by those who are not equipped to do the operation. It is a very delicate procedure, and the general surgeon who attempts an embolectomy once a year, or once in five years, will do more harm than good. If you are equipped and can definitely localize an embolism, as Dr. Allen and also Dr. Veal have done with the use of thorium dioxide, and then can get the clot out with a minimal amount of trauma, much good will result. The procedure should not be attempted unless it is absolutely necessary.

I feel very strongly that the reason we get good results is because we have the full cooperation of our cardiologists. We sometimes see patients even before they have the embolic occlusion, so to speak, that is, at the first indication of pain, and treatment is instituted before I ever see the patient. Consequently, the stage is set for any type of treatment. Passive vascular exercise is certainly not a cure-all; it does help in certain cases to overcome the peripheral vasodilatation, but the scene must be set if it is to accomplish the best results. I try to emphasize this because you are the people who see these occlusions.

No one questioned my statement that approximately 50 per cent of all arterial occlusions did not result in gangrene. I think you can all remember cases in your own experience where an artery has been blocked; a foot has been pale and slightly painful for a while, and then the condition has disappeared. These things must occur more often than we recognize, and so we must say that 50 per cent will not develop gangrene, but it is with those who do develop gangrene that we must concern ourselves most. About amputation, I wish to emphasize again what Dr. de Takats has said, that amputation must be insisted upon early. I have many patients who have survived embolic occlusion because they had early amputation.

Our problem is to tide the patients over these very serious episodes and to save as many legs as we possibly can. It has been a pleasure to be here today and I am glad the surgeons can contribute to the conservative therapy of such important conditions.

Discussion of the paper, "Hypertension Produced by Constriction of the Renal Artery in Sympathectomized Dogs," by Dr. Freeman and Dr. Page.

Dr. Harry Goldblatt, Cleveland, Ohio.—I feel that Dr. Freeman and Dr. Page have made a very important contribution to the study of the pathogenesis of experimental hypertension produced by constriction of the main renal arteries. This demonstration that even total sympathectomy fails to prevent or reduce the hyperten-

sion is the last piece of evidence that was necessary to show that this type of experimental hypertension is not due to a nervous reflex from the kidney and that the nervous part of the vasomotor mechanism does not play a primary or important rôle in its pathogenesis. This centers the initiation of the hypertension upon the reduced blood supply to the kidneys and makes highly probable the existence of a humoral mechanism of renal origin which affects directly the muscle of the arterioles.

Various surgical procedures have been practiced on the nervous system of human beings with hypertension with the idea of reducing the blood pressure. In a certain percentage of cases, no matter what procedure has been used, there has followed a reduction of the blood pressure of varying degree. I see no inconsistency between these positive results and the negative results obtained by the same procedure on this type of experimental hypertension. The two differ in one definite respect. In the experimental type of hypertension the reduction of blood supply to the kidney is effected by reducing the caliber of the main renal arteries by the application of a clamp. In the case of human hypertension the counterpart of the clamp is spasm or narrowing of the renal arterioles due to organic tissue change. No surgical interference with the nervous system can loosen or remove the clamps and improve the circulation to the kidneys. It is only when the clamps are removed or released that the hypertension can and does return to the original level. In the kidneys which are associated with hypertension in man, the musculature of the constricted arterioles might still have the ability to relax in a certain percentage of the cases if the nervous control is removed. This would result in improvement of the circulation through the kidneys. The fall of blood pressure which has been observed may be due to this rather than to an effect on a large part of the vasomotor apparatus in the abdomen.

The fact that these investigators have been able to show that there is no change in the blood volume in this type of experimental hypertension is to me a very significant contribution because it emphasizes the resemblance between this type of hypertension and that which is associated with diffuse vascular disease in man. This means that the study of the pathogenesis of hypertension due to renal ischemia may be of great value because the results may be directly applicable to the pathogenesis of human hypertension.

Dr. Isaac Starr, Philadelphia, Pa.—I would like to say a word about the dangers of using ergotamine tartrate as an agent for discovering physiological facts in survival experiments.

It is well known that ergotamine tartrate in pharmacological experiments will reverse the action of adrenalin. It does not seem to be so well known that the dosages required to produce that effect are generally so large that they do not permit survival of the animal.

In the clinical literature there are numerous reports of attempts to secure sympathetic block by doses of ergotamine tartrate which produced little physiological effect. That such block was actually secured has been assumed too easily. There is an easy control of the situation. Workers using this drug must prove that the action of injected adrenalin is blocked. I have repeated some of the clinical experiments in which it was alleged that ergotamine caused physiological effects by means of blocking adrenine, or adrenalin, and after similar dosage, I could detect no blocking of an injected dose of adrenalin. Therefore, it is obvious to me that people using ergotamine in experiments in which the animal survives, must prove that an injection of adrenalin is blocked, before they can draw physiological conclusions.

Dr. Freeman.—We wish to thank Dr. Goldblatt and Dr. Starr very much for their discussion.

In regard to Dr. Goldblatt's comments, we desire again to emphasize the fact that the central nervous system does not appear to play an essential rôle in the development of hypertension from compression of the renal arteries.

Discussion of the paper, "The Physiological Effects of Extensive Sympathectomy for Essential Hypertension," by Dr. Allen and Dr. Adson.

Dr. Irvine H. Page, New York, N. Y.—I think one must admit that Dr. Allen has presented a very impressive array of evidence, and it illustrates, to my mind, one really significant advance that has been made in medicine today: that is the close, generous and honest cooperation among three men, Dr. Adson, Dr. Brown, and Dr. Allen. I think that is important in view of the fact that in study of a subject like hypertension, where the natural history of the disease is so variable, and the interpretation of the symptoms and signs also lead one astray so easily, these three types of minds are willing to cooperate in an adventure and try to pull out of it something really objective. I feel that they have done this. The Society is to be congratulated in having such a beautiful presentation of just this sort of cooperative adventure.

I may point out that Dr. Adson, Dr. Brown, and Dr. Allen have been pioneers in this field, and this is now the third type of operation in which they have been interested, the first one being section of splanchnic nerves with resection of the lower thoracic ganglia, the second, the ventral nerve root resection, and the third, the operation just described.

Dr. Heuer and I have been interested in the effects of splanchnic nerve resection and anterior nerve root resections, and I think in many ways the results from the latter operation agree to a rather surprising extent with this third operation.

But I feel that the reduction in operative mortality and the fact that this operation is nothing like so serious as the anterior nerve root section is strongly in its favor. Our results with the splanchnic resections have been distinctly disappointing. That is, there certainly is a sharp drop in blood pressure following operation, and in many cases, striking symptomatic improvement. But during the course of the last year or two there has been a definite return not only of the blood pressure back to the pre-operative level, but return of morbid signs and symptoms. Rare patients appear, however, to be benefited by this operation.

Thus we do not feel very optimistic about supradiaphragmatic splanchnic resection. The results of anterior nerve root resection have, on the whole, I think, been about comparable with the results of the operation which Dr. Allen has just discussed. Some results are extraordinary; others, very poor.

The cause of the changes produced in the patient by this operation is obscure. All of us went into it with the definite feeling that the central nervous system was chiefly involved in the genesis of hypertension. I venture to think that we have all learned that the central nervous system is not so important as we had thought in the genesis and maintenance of elevated blood pressure in certain patients.

However, I think that the tendency to discount the importance of the nervous system is distinctly dangerous. We do not know enough about it yet to discard it. Even though Dr. Freeman and I were unable to find any participation of the sympathetic nervous system in Goldblatt's experimental hypertension, this by no means can be transferred to bedside thinking until proof of the identity of experimental and clinical hypertension is forthcoming. I, personally, believe they have

much in common. In watching these patients clinically, one can hardly avoid the feeling—and I must say it is only a clinical hunch—that the nervous system is able in certain patients to precipitate hypertension.

Most of the good results seen are in patients who have shown considerable vascular flexibility; in other words, most of them are relatively early cases. This does not always follow; we have had three patients out of eight with malignant hypertension who have been operated on in whom the results, I must say, are brilliant.

I would like to close with one other matter. It has impressed me, and I think it is quite an interesting scientific point.

You all know that it was a clinical axiom for years that reduction of blood pressure might interfere with the efficiency of renal function. That dates back to Cohnheim and Traube. How much it has influenced physicians in preventing them from attempting to reduce blood pressure, of course, is anybody's guess. However, when the blood pressure is reduced either as the result of these operations, whether it occur spontaneously or whether it be reduced by various medical measures, such as sodium thiocyanate, the renal blood flow, as measured either by urea or creatinine clearance, remains normal. One would have anticipated that, had the hypertension occurred for the purpose of forcing blood through the kidneys, the renal efficiency should suffer if it were reduced. That is not the case.

Furthermore, one might have anticipated insufficient tissue oxygenation throughout the body as a result of sharp fall in blood pressure. That is also not seen. These observations dispose of one of the important objections to reduction of blood pressure as a therapeutic measure, and one of the important modes of thought which have dominated the field of hypertension for many years.

And in closing, I think we have to admit that the Mayo Clinic has contributed importantly to the understanding of hypertension.

Dr. William J. Kerr, of San Francisco, presided at the meeting on Tuesday, June 8. The following program was presented.

GENERAL CARDIAC PROGRAM

Multiple Etiological Factors in 5,000 Cases of Heart Disease in Chicago. Chauncey C. Maher, M.D., and Samuel C. Plice, M.D., Chicago, Ill.

ABSTRACT

The "Criteria for the Classification and Diagnosis of Heart Disease" has been an invaluable aid in directing the current of thought of students of cardiovascular disease toward an etiological classification. In statistical studies regarding the etiological factors in various geographic areas, it has been noted by some authors that in single patients two or more causative factors are present. Some of these combinations are relatively frequent, others less so, and many of them are of considerable practical importance.

In a study in the Chicago area of 5,000 cases from varied sources we have found that fully 30 per cent of the patients present the problem of multiplicity of etiological factors.

Rheumatic fever has been complicated with congenital, bacterial, thyroid, hypertensive, arteriosclerotic, and syphilitic factors. The combinations of the rheumatic fever with the thyroid and syphilitic factors have been our especial interest. Hypertension is complicated most frequently by arteriosclerosis, also by syphilis in the negro and thyroid disease in the white race. Many others might be mentioned.

Further studies have demonstrated that concurrent diseases frequently exist, such as gallstones, duodenal ulcers, anemias, malnutrition, diverticula of the bowel, pelvic disorders in women, and diabetes. The influence of these agents is questionable.

It would appear desirable to present a portion of the data so far obtained to the members of this association for consideration and critical discussion.

The suggestion is offered that the material be presented in symposium form as follows:

I. Summarization of combination of two or more etiological factors in 5,000 cases.

II. Coexistence of rheumatic heart disease with (1) thyrotoxicosis and (2) syphilis.

III. Coexistence of hypertension with (1) other disease entities; (2) thyroid disease; and (3) syphilis.

IV. Coexistence of heart disease with other diseases (noncardiac).

Sixteen Years' Experience With Heart Disease in Pregnant Women. Burton E. Hamilton, M.D., Boston, Mass. To be published.

Some Problems in the Diagnosis, Prognosis, and Treatment of Acute Arterial Occlusion. Harold E. Rykert, M.D., and Duncan Graham, M.D., Toronto, Ont. To be published.

An Injection Study of the Coronary Arteries, Especially in Coronary Occlusion. Monroe J. Schlesinger, M.D., Boston, Mass.

ABSTRACT

The previous development of an anastomotic circulation, coincident with age, has been used to explain the often-noted lack of correlation between fresh or old complete occlusions of the large branches of the coronary arteries and infarcts of the heart.

The incidence of coronary anastomoses has been reinvestigated by a new method, yielding an x-ray picture of all the injectible coronary arteries. These vessels can be studied simultaneously, after projection in one plane without overlapping in the possible anastomotic areas.

These x-ray pictures demonstrate the complete lack of anastomoses in elderly hearts without occluded coronary branches. Other hearts of similar age or younger, without infarcts, in spite of numerous completely occluded branches of the coronaries, show rich anastomoses, bridging gaps in occluded branches, but none elsewhere.

In hearts containing fresh infarcts, definite, but obviously inadequate, anastomotic channels are seen leading to the infarcted area.

On the basis of these observations, it is concluded that anastomoses between branches of the coronary arteries do not increase with the age of the patient, unless coincident with such increase in age, there is also slow occlusion of the branches of the coronaries. Under such circumstances functional anastomoses always develop and to a marked and usually adequate degree.

The Four-Lead Electrocardiogram in Myocardial Infarction and Coronary Insufficiency. Anne Bohning, M.D., and Louis N. Katz, M.D., Chicago, Ill.

ABSTRACT

The four-lead electrocardiograms in twenty-five cases of recent myocardial infarction confirmed at autopsy are presented. The characteristic electrocardiographic variations associated with anterior and with posterior infarctions are demon-

strated. The electrocardiograms in cases with combined anterior and posterior infarctions proved at autopsy are shown to illustrate their tendency to assume certain characteristics of the more recent infarction.

The electrocardiograms in the group of cases of myocardial infarction due to an acute thrombosis are contrasted with those in the group of cases of myocardial infarction associated with the more slowly occluding sclerotic plaques. In the thrombotic group the electrocardiograms show the more striking classically described changes in the S-T and T segments. In the sclerotic group the changes are usually not so typical.

Two hundred consecutive cases with four-lead electrocardiograms in which the initial or serial curves showed changes definitely diagnostic of myocardial infarction were studied. On the basis of the electrocardiographic findings in our own autopsied cases and upon the published reports of other autopsied cases and the evidence afforded by experimental studies, these two hundred cases were classified into the following groups: (1) recent anterior infarction type, (2) recent posterior infarction type, and (3) combined anterior and posterior infarction type. The final classification was not made upon any one finding, but upon the weight of evidence furnished by all four leads and the changes observed in the serial curves. Charts are presented to show the detailed analysis of the type of changes in all four leads for each of these types. The value of Lead IV as a diagnostic aid is demonstrated in a large group of cases, especially those with recent anterior infarctions.

Extracardiac Determinants of the Site and Radiation of Pain in Angina Pectoris With Special Reference to Shoulder Pain. Ernst P. Boas, M.D., and Hyman Levy, M.D., New York, N. Y. To be published.

Syphilitic Aortic Insufficiency: Clinical and Electrocardiographic Studies. L. Minor Blackford, M.D., and Carter Smith, M.D., Atlanta, Ga.

ABSTRACT

Syphilitic aortic insufficiency may develop suddenly by rupture of a gummatous cusp, with death in a few weeks; it may exist at least twelve years without cardiac symptoms. The lesion may be prevented by the prolonged administration of neoarsphenamine in the early stages of syphilis, but it may be precipitated by the injudicious use of this drug in the late stages. The lesion develops sooner after the infection in negroes than in whites. More than half of our patients died within a year after the diagnosis. Of those surviving one year, three-fourths received a large amount of bismuth.

Two or more electrocardiograms were obtained on 50 patients, and single tracings on 80 others. The cardiographic changes paralleled the clinical course in more than half, were directly opposite in about one-tenth, and equivocal in the remainder. The signs of gravest prognosis were splitting and slurring of the QRS complex and progressive low voltage. Arched S-T segments, with high or low take-offs simulating coronary occlusion, were common, but not more common in the group with precordial pain. Finally these electrocardiograms are compared with those of 1,179 patients with other types of heart disease.

Organic and Relative Insufficiency of the Pulmonary Valve. Johnson McGuire, M.D., and Ronald J. McNamara, M.D., Cincinnati, Ohio. To be published.

The Histopathologic Basis of Bundle-Branch Block. Wallace M. Yater, M.D., Washington, D. C.

ABSTRACT

Electrocardiographic manifestations of cardiac conduction disturbances have not been adequately controlled by histopathological studies. Even more confusion exists among the few pathologists who have studied this problem than among physiologists. Between 4,000 and 10,000 serial sections are required to study properly the conduction system of a single heart. A report is made of such a study of several hearts of patients who presented electrocardiographic evidence of intraventricular conduction disturbances. In all cases both bundle branches showed lesions, but one branch was always definitely more involved than the other. The findings in general lend support to the new terminology of bundle-branch block.

Familial Cardiovascular Disease. Jennings G. Olson, M.D., Ogden, Utah. To be published.

The Symballophone: A Modified Stethoscope for the Lateralization and Comparison of Sounds. William J. Kerr, M.D., A. M. Bassett, M.D., M. J. Goldman, M.D., and T. L. Althausen, M.D., San Francisco, Calif. To be published.

Respiratory Changes Produced in the Cardiac Patient by Rebreathing Experiments as Compared With Those of the Normal Individual. Harry Landt, M.D., and Julien E. Benjamin, M.D., Cincinnati, Ohio. To be published.

The Electrocardiographic Changes in Acute Pericarditis: A Clinical and Pathological Study. Joseph B. Vander Veer, M.D., and Robert F. Norris, M.D., Philadelphia, Pa. See AM. HEART J. **14**: 31, 1937.

The Diagnosis and Treatment of Chronic Constrictive Pericarditis. Orrin W. Pineo, introduced by Paul D. White, M.D., Boston, Mass.

ABSTRACT

The author presents his experiences as a victim of chronic constrictive pericarditis.

In May, 1935, he began to have dizzy spells on exertion, slight dyspnea, and epigastric tenderness. In July, 1935, he noticed that his collars were tight and the veins in his neck were swollen. In August swelling of the lower legs appeared, and he noticed that his belt left an imprint on his abdomen. Digitalis was prescribed in October, but it was of no benefit.

For this condition the author presented himself to several physicians. The diagnosis of congestive heart failure was made, and treatment for such a condition was begun, but there was little or no gain except temporarily by rest and the vigorous use of diuretics. Finally, in October, 1936, one and one-half years after the onset of symptoms, it became evident that chronic constrictive pericarditis was the cause of the trouble.

Physical examination showed engorgement of the liver with ascites and dependent edema and increased peripheral venous pressure as indicated especially by prominence of the neck veins and a venous pressure of 23 cm. The electrocardiogram showed normal rhythm, rate 80, with low voltage in all leads, including the chest lead, and slightly inverted T-waves in all leads.

Fluoroscopy showed the heart normal in size and shape. The right border was hazy and poorly defined without visible pulsation. The pulsation of the left border was rather feeble. There was a slight amount of fluid at the right lung base.

On Oct. 8, 1936, Dr. Edward D. Churchill, of Boston, resected the pericardium, and in the course of a few weeks the author lost all evidence of his congestion. Since then he has been perfectly well. The venous pressure measurement on Feb. 19, 1937, was 10 cm.

Acute and Chronic Compression of the Heart (with motion picture demonstration). Claude S. Beck, M.D., Cleveland, Ohio. To be published.

Fainting Attacks Resulting From Hypersensitive Carotid Sinus Reflexes (with motion picture demonstration). Harry L. Smith, M.D., Rochester, Minn. To be published.

The Use of Quinidine Sulphate Intravenously in Ventricular Tachycardia. John Hepburn, M.D., and Harold E. Rykert, M.D., Toronto, Ont. To be published.

The Precipitating Causes of Congestive Heart Failure. William A. Sodeman, M.D., and George E. Burch, Jr., M.D., New Orleans, La. To be published.

A Clinical Study of a Preparation of Squill (Urginin) in the Treatment of Myocardial Insufficiency. Francis L. Chamberlain, M.D., and Robert L. Levy, M.D., New York, N. Y. See AM. HEART J. **14**: 268, 1937.

A Study of the Renal Arteries in Relation to Age and to Hypertension. Robert H. Williams, M.D., and Tinsley R. Harrison, M.D., Nashville, Tenn. To be published.

DISCUSSION

Discussion of the paper, "Multiple Etiological Factors in 5,000 Cases of Heart Disease in Chicago," by Dr. Maher and Dr. Plice.

Dr. Julien E. Benjamin, Cincinnati, Ohio.—Will Dr. Maher please state his criteria for the diagnosis of psychoneurotic and neurotic patients?

Dr. Paul D. White, Boston, Mass.—May I add a note on this important and interesting subject, with particular reference to the pulmonary factor. We must carefully distinguish the cor pulmonale, true pulmonary heart disease, which so far as we know is rare although it may be more common than we think at present, from pulmonary symptoms due to congestive failure of the left ventricle, from mitral stenosis with pulmonary congestion, and from pulmonary disease itself. These three types of pulmonary disturbance in connection with heart disease are important to study further. Perhaps as important as any other point would be the more careful judgment of the factors of strain on the right ventricle. Until we have adequate measurement of the true size of the right ventricle, especially its weight, we do not know how common the cor pulmonale is.

Dr. Maher.—The Criteria for the Classification and Diagnosis of Heart Disease was used in classifying patients with psychoneuroses. Many of these patients were also examined by a psychiatrist. This group included patients with neurocirculatory asthenia and cardiac neuroses.

Discussion of the paper, "Sixteen Years' Experience With Heart Disease in Pregnant Women," by Dr. Hamilton.

Dr. Louis A. Kapp, New York, N. Y.—Dr. Hamilton's contribution is of great practical importance to the problem of management of cardiac patients in pregnancy.

Due to the difficulty in the proper evaluation of some clinical signs and symptoms during pregnancy, attempts have been made to approach this problem from several

angles. Dr. Pardee, of New York, some time ago recommended that the functional capacity test, based on the response of cardiac patients to a certain amount of exercise, be used as a guide in the management of these cases. Dr. Hamilton evidently bases his classification, which is entirely different from the classification advised by the New York City Heart Committee, on the physical findings and laboratory tests.

Each of these methods has its advantages and disadvantages. Dr. Pardee's method is very simple and can be carried out easily in practice. It has, however, many subjective or personal elements. In addition, the classification based on functional capacity is often too changeable: many women entering pregnancy as Class I, may in a few months become Class IIa, and finally, at the end of their term or during labor, be reduced to Class IIb, or III. Furthermore, I have seen cases of Class IIa suddenly developing acute left ventricular congestive failure during labor. On this point I must disagree with Dr. Pardee, who believes that "such things do not happen unexpectedly when the functional capacity grouping is used." The picture of a woman in labor, suffering from pulmonary edema, is so distressing that everything must be done to prevent such a grave condition.

Dr. Hamilton's method is probably more accurate, but it requires a great deal of technical work. Dr. Hamilton uses a more strict and dependable regimen, and I believe, in applying it, we might be able to prevent some of the dangerous cardiac complications in pregnant patients. I do not see, however, why both methods cannot be combined, supplementing each other, and furnishing sufficient criteria for the adequate control of the individual cases.

I should like also to say a few words on the value of full digitalization of patients with signs of congestive failure during pregnancy. I feel that in many cases a serious or fatal breakdown of the circulation is due to insufficient digitalization. If we endeavor to obtain better results, the digitalis treatment should not be left to the obstetrician alone, who is often inclined to use too small and ineffective doses of the drug; strict supervision is necessary. I, therefore, believe that special care and cooperation between the obstetrician and cardiologist in the management of these cases will be helpful in reducing the maternal mortality rate in cardiac patients.

Dr. Hamilton.—I am glad Dr. Kapp brought up the subject of classification and of effort tests and thank him for his discussion.

Our classification is an outcome of examination of recruits in the World War. The first problem then was to decide what physical signs justified the diagnosis of a seriously damaged heart in a young man and made him unfit for full military service. The criteria for our Class I proved sound for soldiers and have proved sound in selecting women for the risk of pregnancy. Recognizable heart failure does not occur in young adults except among the Class I cardiac subjects. The great variety of factors influencing prognosis in pregnancy has kept us from having confidence in any finer subdivisions of Class I except for the subdivision which we happen to call Class Ia. With improving care in the treatment of Class I cardiacs, the need for further classification in pregnancy seems to disappear, while the need for stubborn, continuous supervision of the individual cases becomes more evident. There need be no serious conflict between this classification and the New York classification, provided those using the New York classification apply it to young adults who have the criteria (as for our Class I) which determine that they have in fact seriously damaged hearts. The New York classification does not define the young adult who should be considered a cardiac. As it stands, it suggests that young adults can be classified in respect to their hearts by their functional ability

alone. This allows for confusion in reporting data since only those who are clearly Class I by our criteria have need for any interest in the response of their hearts to pregnancy. The more than ninety-eight per cent of pregnant women who are not Class I never die from causes attributable to the heart.

The results of effort tests vary so greatly under changing conditions—fatigue, anemia, infections, weight changes, fluid intake—that it seems to me that we can hardly expect them to be reliable guides in the prognosis of pregnancy to which so many factors contribute; and that their chief informative value is to show us the importance of these factors in disability and thereby direct our attention to protecting our cardiac patients against such controllable causes of heart failure.

Discussion of the paper, "An Injection Study of the Coronary Arteries, Especially in Coronary Occlusion," by Dr. Schlesinger.

Dr. William J. Kerr, San Francisco, Calif.—This is one of the most important papers on our program today. Dr. Schlesinger has shown us a very ingenious method of displaying the circulation of the heart. I should like to ask Dr. Schlesinger one question, that is, whether he has had any difficulty in injecting accessory coronary vessels or small ones that come off near the origin of the coronaries.

Dr. Merritt B. Whitten, Dallas, Texas.—Dr. Schlesinger certainly has made a decided advance in injection of the coronary arteries. He has made a definite improvement of the method of Gross and Spalteholz, and when I see his illustrations I recall some by Spalteholz, who illustrated the coronary circulation by diagrams somewhat similar to these of Dr. Schlesinger, but apparently did not actually roll out the heart as Dr. Schlesinger has done.

This new method has the advantage over any method which we have yet seen in that with it we can definitely see anastomosis. Everyone has realized that there are anastomoses in the heart. One can inject one coronary artery alone, and in some cases fill the other coronary artery entirely, showing that there is anastomosis, but actually to find the vessel has been a difficult problem. I agree with Dr. Schlesinger that the trouble with Gross' method is that the overlapping of the vessels makes it difficult to tell whether two vessels cross each other or actually anastomose. With the corrosion method, most of the anastomoses are destroyed, but with this new method it seems that we can actually see them.

There are two or three technical difficulties we have to consider in any injection method. If there are post-mortem clots remaining in any of the vessels, these may obstruct the flow and prevent complete injection of the arterial tree. Furthermore, with multiple injections it is important that the injection of the two vessels be simultaneous, otherwise, the injection mass may quickly run through from one artery to the other, and it becomes difficult to locate the anastomotic vessels.

I think this method is a decided advance in our study of coronary occlusion and should be used much more extensively at post-mortem examinations.

Dr. Robert L. Levy, New York, N. Y.—Dr. Schlesinger's specimens are of great interest in that they portray in graphic fashion many episodes which can be translated into clinical phenomena. I shall only touch upon two. One is the variability in clinical symptoms, which can be readily understood on the basis of these beautiful injections. There takes place, for example, occlusion of a vessel or vessels, which is associated with discomfort; this is followed by the establishment of collaterals, with improvement. Later, there may be closure of other branches, with accentuation of anginal pain. Such a sequence has an important bearing on the attempt to appraise the value of any therapeutic measures which are applied to patients with cardiac pain because it explains the tendency to spontaneous variations in the symptomatology.

The second point is related to the specimen shown in which there were multiple areas of occlusion without infarction; sudden death occurred, presumably as a result of the rupture of an atheromatous ulcer. This case illustrates the fact that the heart can carry on although the reserve of the coronary circulation is greatly reduced; but if, superimposed upon such vascular impairment, a sudden accident takes place which further diminishes the reserve to only a small fraction of normal, there results what we have termed "acute, fatal coronary insufficiency." But sudden death is not necessarily associated with the formation of a thrombus or an infarct; dysfunction may be induced by any cause which brings about insufficiency of the coronary circulation. The terminal incident is frequently, but not always, ventricular fibrillation.

Dr. Schlesinger.—The question was asked as to the injection of the accessory circulation by this method. In several of the hearts with spontaneous pericardial adhesions, there was no injection outward into the adherent pericardium when the mass was injected into the coronary arteries.

The question of post-mortem clots obstructing the circulation of the mass is very easily checked up on each heart. We always make a complete dissection of the coronary arteries in these hearts after they have been injected. This dissection is absolutely necessary to show which color mass has gone into which vessel and where they have mixed. In this dissection we uncover all ante-mortem and post-mortem clots.

The question about the effect of simultaneous injection of both vessels on the flow from one to the other is an important one. We always start the injection of both vessels simultaneously, slowly raising the pressure to 150 millimeters of mercury and keep it there until it stays constant at that point. Then in all these hearts, in order to disclose any anastomosis which may be present, we lower the pressure on one side to zero, or below, maintaining that in the other coronary at 150 millimeters of mercury, and then reverse this process. When there are no anastomoses present between the two sides, even this extremely unphysiological relation between the two vessels will not force the injection mass from one side to the other. In the 22 normal hearts without anastomoses the same process of reversing and unbalancing the two coronaries was carried out without flow from one side to the other. Of course, at the site of vessels where there are anastomoses, this helps drive the mass from one side to the other.

The question of whether the heart does not really carry on because of the newly developed anastomoses and compensatory circulation is of interest not only in the hearts with occluded vessels. Although I did not bring them along to this meeting, we have a few hearts with enlargement from other reasons, such as hypertension, rheumatic fever, etc., in which there also is a certain degree of anastomotic circulation established in the absence of any occluded vessels. Thus anastomosis between the coronary vessels can occur without occlusion if there is a need in some part of the heart for more blood. This sequence is not as constant as that following the presence of an occluded vessel. We have not had a large enough number of this type of case to say exactly in which condition anastomoses occur, but we feel that anastomoses between coronary arteries always indicates a pathological heart.

Discussion of the paper, "The Four-Lead Electrocardiogram in Myocardial Infarction and Coronary Insufficiency," by Dr. Bohning and Dr. Katz.

Dr. Sidney P. Schwartz, New York, N. Y.—Dr. Bohning would have us believe that it is possible by means of serial electrocardiograms to differentiate between a patient with myocardial infarction as a result of an acute coronary vessel closure and a patient with fibrotic replacement of the heart as a result of atherosclerotic narrowing of the vessels supplying that particular region.

As a controlled series for a study of this type, it would be essential to obtain serial electrocardiograms over a period of years on patients with hypertension and enlargement of the left ventricle, to follow such patients to the autopsy table, and to note whether underlying pathological lesions can be correlated with the electrocardiograms obtained. I mention patients with hypertension as controls because the electrocardiogram associated with enlargement of the left ventricle in the course of hypertension would appear from the few studies available to date to show changes somewhat similar to those which Dr. Bohning has presented today as characteristic of patients with myocardial fibrosis.

We have obtained serial electrocardiograms over a period of years on twenty-five consecutive patients with hypertension and enlargement of the left ventricle that have come to autopsy. The electrocardiograms obtained by us are almost identical with those which Dr. Bohning has associated with fibrotic replacement of the heart muscle in the presence of atherosclerotic involvement of the coronary vessels. However, in none of our cases was there either fibrotic replacement of the heart muscle or any lesions of the coronary vessels.

Consequently, I do not believe that on the basis of such observations it is possible in the majority of cases to differentiate from the electrocardiogram those patients who have only enlargement of the left ventricle without coronary vessel involvement from similar cases with fibrotic replacement of the muscle. There is no doubt in my mind from correlated studies to date between the clinical investigations, the electrocardiograms, and the underlying pathological lesions that when infarction or fibrotic replacement of the heart muscle takes place, we have in most instances a very definite pattern in the electrocardiogram such as is well known. Dr. Bohning's ideas, however, remain yet to be proved.

Dr. Arthur M. Master, New York, N. Y.—Some of the difficulties of correlating the electrocardiographic findings and even the clinical findings with the pathological findings can be brought out by our experiences recently. We have done what Dr. Saphir and his collaborators suggested. We reviewed some 79 hearts that came to autopsy following death from coronary artery occlusion, and at the suggestion of Dr. Paul Klemperer and Dr. Louis Gross we reexamined and rechecked 42 of the hearts. We made very frequent cross-sections of the coronary arteries throughout their entire course, and in these 42 hearts where previously some 80 occlusions had been reported we actually found 105. We found that even when an acute occlusion is present, 40 per cent had not only one but at least two acute occlusions. We found that where previous occlusions were present, in 80 per cent of the hearts there were at least two or three previous occlusions. The multiplicity of occlusions illustrates the difficulties of correlating the electrocardiographic findings with the location of infarcts. On the other hand, in the majority of cases we had the same experience that Dr. Bohning had. There was correlation. We found, as Barnes has and as Whitten has, that the left anterior descending should not be called the artery of occlusion; that the right artery is as frequently involved as the left; that the posterior surface is as frequently affected as the anterior surface.

Dr. Bohning.—In answer to the first question, I think a differentiation should be made as to the electrocardiographic changes related to acute or subacute myocardial injury and those due to chronic myocardial involvement. Most authorities agree that the S-T deviation is related definitely to changes involving the myocardium. The changes due to enlargement and the changes due to the placement of the heart in the chest are, I think, more often related to variations in the form of the T-wave and the QRS complex.

We have made studies with multiple chest leads, going entirely around the chest in a number of cases, both with normal and with injured hearts, and these seem to indicate that there is a great deal yet to be said concerning variations in the electrocardiogram due to changes in the size and position of the heart. We can definitely say, however, that the marked S-T deviation seems to be related to an acute or subacute change, particularly when these deviations tend to decrease or to disappear.

We have also seen a number of cases with myocardial infarctions, especially those with multiple infarctions, in which we could not without earlier curves or an autopsy make a definite diagnosis as to the type of infarction. In our series we had 73 cases of posterior infarct type and 119 cases of anterior infarct type, which would seem to indicate a more frequent involvement of the left coronary artery, but in some of our autopsied cases the right coronary artery was also involved although only anterior infarction was present. Experiments have shown that constriction of the left anterior descending coronary artery produces a relatively greater decrease in total coronary outflow than constriction of the right coronary artery. Therefore, it seems probable that the area of myocardium supplied by the right coronary artery has in most individuals a better collateral circulation than that supplied by the left coronary artery.

Discussion of the paper, "Extracardiac Determinants of the Site and Radiation of Pain in Angina Pectoris With Special Reference to Shoulder Pain," by Dr. Boas and Dr. Levy.

Dr. Emanuel Libman, New York, N. Y.—There is a great deal that might be said in connection with this careful and scholarly paper of Dr. Boas and Dr. Levy.

In the first place it is very interesting that they have shown statistically that in the cases of shoulder pain complicating cardiac pain due to coronary artery disease, the pain is mostly on the left side. I am glad that Dr. Boas referred to the exceptions.

How are these shoulder pains brought about? My own idea, for a number of years, has been that there is a metabolic disorder underlying coronary artery disease and coronary thrombosis and that the same (or a similar) disorder plays an important rôle in the pathogenesis of many cases of bursitis, spondylitis, gallbladder disease, eczema, etc. Patients who suffer from coronary artery disease, not infrequently have previously suffered from a shoulder disturbance, usually with limitation of motion. A coronary attack may intensify the condition. In other cases, the shoulder disorder exists in a mild or latent form, and then real suffering is brought about by irradiation (or sensitization) as Dr. Boas has pointed out, when the patient develops the cardiac pain. It is of interest, in this connection, to note that the same sequence of events is occasionally encountered in cases of gallbladder disease, the shoulder difficulty then being on the right side.

What I have said sounds strange, but, if one thinks a bit about it, the impression is a different one. If anybody asks you what is the cause of general arteriosclerosis (atherosclerosis) you will say, if you follow the usual teachings, tension and a metabolic disturbance. The same must hold true for the arteries of the heart.

A patient suffering from the shoulder difficulty which Dr. Boas has so fully discussed, may, if he is hyposensitive to pain, suffer from weakness, with or without paresthesias, instead of pain. It is important to know that the therapeutic maneuver which I employ does not act by decreasing the sensitivity of the nerves. This is demonstrated by the experience that when numbness or weakness is the outstanding symptom of the disorder and not pain, and the method is effective, the whole extremity becomes stronger and any numbness diminishes or disappears.

I feel that I ought to say something about the method itself. I believe it to be valuable, and I am grateful for having found it because it so often relieves suffering.

Firm pressure is applied to Erb's point for about one minute. In some cases less than one minute suffices, in occasional cases a somewhat longer duration of pressure is desirable. After the pressure is released, the patient rests for a minute or two to allow for any pain due to the pressure itself to disappear. Then the patient is asked to raise the arm, and very frequently spontaneous pain is no longer present. This relief may last for hours, days, weeks or months, or for good, even though the original condition persists. The maneuver can be applied repeatedly. If both arms are involved, both sides must be treated separately. It is important, as Dr. Boas has also suggested, to learn how useful the method may be in distinguishing pain in shoulder disorders and those due directly to the heart.

I cannot yet state through what mechanism this maneuver gives the results, but I think that we will find that an effect upon the autonomic nerves plays a rôle. The importance of learning the exact mechanism is self-evident.

Dr. William J. Kerr, San Francisco, Calif.—I should like to ask Dr. Boas whether he has studied the relative position of the two shoulders in these patients and whether an encroaching thoracic condition, such as increasing pulmonary emphysema, could play any rôle in the production of the pain.

Dr. Boas.—I have not paid particular attention to that point, but as I recall the cases I do not believe that such factors as Dr. Kerr mentioned play a rôle in this syndrome.

I have been rather struck by the absence of similar shoulder pain in gallbladder disease although I have looked for it. By analogy, as Dr. Libman suggested, one might expect to find it. While these patients often complain of pain in the trapezius muscle, they do not have this pain in the shoulder which prevents them from moving the arm.

Discussion of the paper, "Syphilitic Aortic Insufficiency," by Dr. Blackford and Dr. Smith.

Dr. Paul D. White, Boston, Mass.—For some of us in the North who have had much less experience than Dr. Blackford in the diagnosis and prognosis of cardiovascular syphilis his figures may seem a little hard to believe, but I have visited his clinic in Atlanta and can vouch for at least some of these cases. Incidentally, for the first time I heard there a considerable number of Austin Flint murmurs in a single day.

Dr. Harold S. Feil, Cleveland, Ohio.—Occasionally one finds patients with evidence of syphilitic aortic insufficiency clinically, and the post-mortem examination reveals cystic medial degeneration with dilatation of the aortic ring. This pathological condition was described by Erdheim and by Moritz. Within the past year, two such patients were observed at the Lakeside Hospital—one patient had latent syphilis and the other patient was nonsyphilitic. Both were young individuals. One cannot say that every patient with free aortic insufficiency and a positive Wassermann has syphilitic aortic insufficiency without bearing this interesting pathological condition in mind. The possibility of its presence should be especially stressed in patients without other evidence of syphilis.

Dr. Blackford.—These patients all had syphilis and all free regurgitation at the aortic valve. So far as possible, we fluoroscoped them to exclude calcification of this valve. We believe the error of diagnosis is very low.

Personally, we have only made the diagnosis of dissecting aneurysm of the aorta once (an account of the case will appear in the *Journal of the American Medical Association*), but other physicians at the Grady Hospital have done so four or five times. We are sure that, in spite of the to-and-fro murmur which may be heard in such cases, we have not counted any such as syphilitic aortic insufficiency.

Discussion of the paper, "Organic and Relative Insufficiency of the Pulmonary Valve," by Dr. McGuire and Dr. McNamara.

Dr. William J. Kerr, San Francisco, Calif.—Dr. McGuire has presented a very interesting subject and has done it very well. I should like to make a brief remark concerning the murmurs and organic pulmonary insufficiency.

In a limited experience with this type of clinical condition, we have observed a diastolic murmur which Dr. McGuire mentions and have found that it passes down along the sternum more definitely than it does toward the left axilla. Often it is heard best at the xiphoid process, or near there. In addition to the rumbling diastolic murmur, there may be a presystolic murmur which is very much like the Austin Flint murmur heard in aortic insufficiency and also in relative pulmonary insufficiency; with the Graham Steele murmur there may be a murmur of very low intensity heard near the lower end of the sternum, which is also presystolic in time and similar to the Austin Flint. I think that we should keep these murmurs in mind and examine patients for them and try to differentiate them from the murmurs of aortic insufficiency.

Dr. Maude E. Abbott, Montreal, Canada.—I am afraid I have not a great deal to add to this subject, for the reason that this is a relatively little explored field of congenital heart disease, at least from the statistical standpoint. We are only beginning now to assemble data upon it.

I was very much interested to see last autumn in Dr. Kerr's own service at the University of California Hospital a remarkable case of aneurysmal dilatation of the pulmonary artery with insufficiency and some stenosis of the pulmonary valve. The etiology of the tremendous dilatation of the pulmonary tract was not clear.

I think the general impression about this type of lesion in this situation is that there is usually some localizing factor that leads to the incidence of an infective process on the pulmonary cusps, or to the occurrence of a relative or organic pulmonary insufficiency. I noticed in the picture of the post-mortem appearances of the second case what looked very like four pulmonary cusps, and I wonder if that might be the underlying factor here in the development of the pulmonary regurgitation.

The subject of pulmonary atherosclerosis is one that is becoming more and more interesting from the standpoints of congenital as well as acquired conditions, and there is still much to be learned in this field. The contribution made by Dr. Roessler to its x-ray study is very important. It is interesting that the second case was, I believe, diagnosed radiologically by him.

I think that is all I have to add, Dr. Kerr. It was very kind of you to give me this opportunity of meeting this assembly on a congenital cardiac topic.

Dr. Emanuel Libman, New York, N. Y.—This very interesting demonstration has a number of points of importance. In connection with one of the reported cases, I would like to refer to the case described many years ago by Dr. Edward G.

Janeway. It was a case in which he had clinically diagnosed gonococcal infection of the pulmonary valve. The patient recovered from the infection but was left with pulmonary regurgitation. Perry has reported a similar observation (1930-1933).

I would like, for a few minutes, to take up the subjects of rheumatic lesions of the pulmonary valve, and the Graham Steele murmur. Dr. McGuire has mentioned the work of Epstein and Kugel and that of Dr. Louis Gross. They showed that rheumatic involvement of the pulmonary valve was not as uncommon as was generally believed, the lesion being much more marked in the ring than in the valve flaps. The two cases reported by Dr. McGuire are most unusual because there is present a real rheumatic valvular lesion.

One must be very cautious in predicating the presence of a Graham Steele murmur. I can emphasize that by telling you of a case which I once presented to Dr. Osler, and concerning which he said, "This patient has a Graham Steele murmur, and this is the first one I am at all sure of." The post-mortem examination revealed an aortic insufficiency. When one finds this diastolic murmur which is considered to be evidence of relative pulmonary insufficiency, it is important to examine the valve carefully for predisposing conditions such as thickening or a congenital anomaly of the valve cusps.

Dr. L. Minor Blackford, Atlanta, Ga.—Some twenty-five years ago, someone announced that dilatation of the pulmonic conus or trunk was a sure sign of a patent ductus. This statement has been copied blindly in many textbooks.

Actually, almost all of the few proved cases of patent ductus with dilatation of the pulmonic artery have had other anomalies to explain the dilatation. In most cases of dilatation of the pulmonic artery, as in the seven Dr. McGuire has just reported, the ductus is normally obliterated.

Dr. McGuire.—I should like to thank Dr. Kerr for explaining the pseudo "Austin Flint" murmur we heard in Case 9.

With regard to the question of congenital lesion of the pulmonary valve that Dr. Abbott has spoken of in the second case, it is our belief that the removal of part of a cusp for section produced an artefact which simulates an extra leaflet. There was nothing to suggest congenital malformation in the original specimen.

Discussion of the paper, "The Histopathological Basis of Bundle-Branch Block," Dr. Yater.

Dr. Louis A. Kapp, New York, N. Y.—I note that one of the cases presented by Dr. Yater showed transient asystole with Adams-Stokes attacks. I have also observed at the Bronx Hospital several such cases in which no A-V heart block was found.

I wonder whether the mechanism of production of these attacks cannot be explained by the observation made by Dr. Yater that in practically all cases of bundle-branch block both branches show distinct pathological changes, one branch being usually more affected than the other. When, for some reason, in the less affected branch a severe obstruction in the conduction suddenly develops, the block becomes complete, with possible Adams-Stokes syndrome.

I think that this cause of Adams-Stokes disease should always be considered in the absence of auriculoventricular conduction defect.

Dr. Paul D. White, Boston, Mass.—I would like to congratulate Dr. Yater on a very important and difficult job. He has made a distinct advance in our knowledge of bundle-branch lesions and bundle-branch block, even though the last word may not yet have been said.

Discussion of the paper, "Familial Cardiovascular Disease," by Dr. Olson.

Dr. May G. Wilson, New York, N. Y.—I think perhaps it might be of interest to report that in a recent study of rheumatic families, we found on genetic analysis of the data that the susceptibility to rheumatic fever was transmitted as a single autosomal recessive gene. The very interesting report of Dr. Olson is of extreme importance.

Dr. Olson.—One thing that I plan to do is to report on this family at ten-year intervals. It appears from a study of the first four generations, at least, that the age of onset of the angina is decreasing. I do not at the present time have in this family any record of angina occurring in the third decade, that is between twenty and thirty years. I mentioned the situation in the third generation, most of whom are now living and three definitely had onset in the early thirties.

With respect to the occurrence of rheumatic disease in families, I learned with a great deal of surprise that in Chicago there exists the impression that rheumatic fever does not occur in families. I have had in my practice forty-seven instances of rheumatic disease occurring in the families of mothers who had it.

Discussion of the paper, "The Symballophone: A Modified Stethoscope for the Lateralization and Comparison of Sounds," by Dr. Kerr.

Dr. Howard B. Sprague, Boston, Mass.—We had the privilege at the Massachusetts General Hospital of having a demonstration of this instrument by Dr. Kerr some weeks ago, and we were very much impressed with its possibilities. There is one detail that Dr. Kerr might like to mention, and that is, if you have any difficulty in being convinced of what the instrument will do, you must first demonstrate that your hearing is equal on the two sides. Many of us do not realize until we attempt to use an instrument of this sort that the auditory acuity is different on the two sides. I made the unhappy discovery that my hearing was not the same on the two sides, and therefore I had a little difficulty at first in discovering the potentialities of the instrument.

Dr. Julien E. Benjamin, Cincinnati, Ohio.—I may be a little stupid, Dr. Kerr, but I do not quite understand why one could not simply attach one end of the stethoscope to one ear and the other to the other ear. Will you explain again why both must be attached to each ear?

Dr. Paul D. White, Boston, Mass.—I should like to ask Dr. Kerr when this new instrument will be available for our general use.

Dr. Kerr.—Dr. Sprague brought up a point which, of course, is important. If one hears with only one ear, then he might just as well have an ordinary, old-style, monaural stethoscope such as Laennec introduced, and under those circumstances the sound which one hears appears to be directly in the ear.

The binaural stethoscope throws the sound out in space some distance in front of us, and one does not have a loud noise directly in the ear. If the ears are unequal, it would probably throw the sound to one side or the other with this type of stethoscope. It would seem to come from one side or the other, but it would not be any more of a handicap than we have with the ordinary stethoscope.

The question was asked about the direct tubes. If one listens to sounds with direct tubes to the two ears, the sound seems to arise directly in the two ears, and ordinarily it is very annoying. If the sound is of any intensity, it is confusing,

and we have found it difficult to determine small differences with it. We are giving demonstrations at the scientific exhibits and will be pleased to demonstrate this and other points to Dr. Benjamin and others who wish to attend.

I should like to pass around two little membranes or disks which we obtained with two different endpieces for stethoscopes. If you are making up one of these instruments, which you may do rather simply, be sure that the vibration rates of these disks are identical or that they are very close to each other. I am going to pass these around and if you listen with the two, the sounds would be dissimilar.

The instrument is not yet being made and will not be made until we are very certain on all the psychological points. We have most of these cleared up now, but we do not want to put anything out until we know it is reliable, and then we will insist that it be put out at a very low cost. It should not be much more expensive than the ordinary binaural stethoscope.

Discussion of the paper, "The Electrocardiographic Changes in Acute Pericarditis," by Dr. Vander Veer and Dr. Norris.

Dr. Charles C. Wolferth, Philadelphia, Pa.—Dr. Vander Veer's finding of a correlation between his electrocardiographic changes and myocardial injury is very important. That is not the point, however, that I wish to discuss.

There are at least two clinical conditions in which chest leads should be made in the anteroposterior position as well as with one electrode on the apex and the other electrode on the left leg. Acute pericarditis is one of them. The other is infarction that extends around either from the anterior to the posterior surface of the heart, or vice versa.

The reason, I think, the chest lead selected by Dr. Vander Veer and his colleagues for this study failed to be of much value is that in pericarditis, as a rule, both the anterior and posterior surfaces of the heart are involved. In that particular type of lead, under these conditions, the deviations of the RST segment caused by anterior and posterior injury tend to neutralize each other. If, however, an anteroposterior chest lead is made, the summation of RST segment deviations tends to occur so that one obtains deviations which are frequently much greater than those recorded in limb leads.

Dr. Roy W. Scott, Cleveland, Ohio.—It is now ten years since Dr. Feil, Dr. Katz and I first observed that changes in the ventricular complexes similar to those found in myocardial infarction occurred in patients with pericardial effusion. Both clinical and experimental evidence indicated that the hydrostatic pressure in the pericardial sac was an important factor in distorting the curves. While it seems likely that in certain cases of pyopericardium the associated inflammatory changes in the myocardium may affect the electrocardiogram, I do not believe that in the light of past observations one is justified in concluding that pericardial effusion per se may not cause characteristic changes in the ventricular complex of the electrocardiogram.

Dr. Vander Veer.—I appreciate Dr. Wolferth's discussion because he is an authority on the chest lead. There is no question but that Lead V gives a summation effect, as does Lead II, which tends to diminish the changes which one may obtain in the chest lead in this type of case. However, from the practical standpoint, one cannot take three or four chest leads, and it may be, as I think Dr. Wolferth does, a better plan to take Lead IV than Lead V as we have done. We have taken Lead V because it is handier. The patient lies in bed and does not have to roll over or move.

Fundamentally, however, we can differentiate these cases from myocardial infarction without the Leads IV, V and VI because they do not have the patterns that one would expect with a large infarction which involves both anterior and posterior surfaces. So, from the clinical standpoint, if one is aware of the typical pattern, one can diagnose it from the electrocardiogram with the other findings.

Dr. Scott has mentioned their findings of many years ago, and it is certain that the subject is not completely settled. However, I believe that a great deal of evidence points to the association of the electrocardiographic changes with myocarditis. One may see a patient with extreme cardiac tamponade from hemopericardium. The heart cannot be heard, and there is no pulse, but there is a normal electrocardiogram. Certainly, if a tamponade was going to produce an insufficiency of coronary flow, it would produce it in those cases. The same patient may be operated upon, and the pericarditis pattern may follow in two or three days. While I agree that the subject is not settled, I believe that in most cases the changes in the electrocardiogram are due to myocarditis.

Discussion of the paper, "The Diagnosis and Treatment of Chronic Constrictive Pericarditis—Orrin W. Pineo," by Dr. White.

Introduction by Dr. P. D. White

Mr. O. W. Pineo, a physicist, now twenty-nine years old, has been so kind as to come here today to tell you briefly of his personal experience with constrictive pericarditis and its treatment. He is, to be sure, an outstanding example of the curability of the disease, but as such is far more important for you to see than one of our failures. We have been unusually fortunate in having the majority of the cases of our series resemble him in most respects. His own story he will give you. I shall simply read to you, in closing my introduction of Mr. Pineo, the operative notes written by my surgical colleague Dr. E. D. Churchill early last fall.

"A thick calloused pericardium almost completely adherent to the heart was found at operation. A good line of cleavage was established and ventricles and right auricle were decorticated anteriorly with the freeing of the heart from the diaphragm. Fluid was aspirated from both pleurae. The operation lasted two hours and fifty minutes. He left the operating room in good condition.

"Pathological examination of the excised pericardium showed chronic inflammation without evidence of active tuberculosis or rheumatism. There was no calcification."

Discussion of the paper, "Acute and Chronic Compression of the Heart," by Dr. Beck.

Professor Jacobaeus, Stockholm, Sweden.—Mr. Chairman, Ladies and Gentlemen, I first bring you my warmest thanks for introducing me to this meeting. I have heard Dr. Beck's paper with the greatest interest. The condition and the operation are of great interest to us in Sweden, and while we have performed this operation, we have not seen so many cases as you have. I shall take home to our surgeons encouragement to continue this work and to continue their interest in internal medicine. Thank you very much.

Dr. C. Sidney Burwell, Boston, Mass.—The first of Dr. Beck's observations which I wish to emphasize is that pericardial obstruction is not a particularly rare condition. Moreover, it is a condition which it is of the greatest importance for physicians to recognize, since, as Dr. White and his colleague-patient pointed out, it is in many instances amenable to skillful treatment. The logical process which

Dr. Beck recommends, of recognizing a physiological mechanism and proceeding from that recognition to a consideration of a disease process, is, I should say, one which is utilized by most of the people who have wide experience with this disease.

Now I should like to ask Dr. Beck his opinion about one point which is not always made clear in descriptions of a disease or descriptions of operative treatment. This question is concerned with the place in the circulation at which the obstruction occurs. When the pericardium is filled with fluid, it is obvious that the compression of the heart is exerted generally. It must involve the ventricles, the auricles, and the intrapericardial portions of the vessels. One sometimes gets the impression from reading the older literature that the obstruction from scar often comes about through constriction of one of the vena cavae. If constriction of the venous channels were important, one would expect to find occasionally a difference in the pressure in the inferior vena caval as compared with the superior caval system. In a considerable number of cases in which comparable measurements have been made, we have not seen a case in which such a difference existed except when some obvious local cause for it was present.

If I understand Dr. Beck's description, it implies that he considers the important point of obstruction to be in the pericardial scar involving the ventricles themselves. This agrees with the general concept that the difficulty in constrictive pericarditis is the inability of the ventricle to dilate adequately. If this theoretical concept is true, it should be demonstrable by a simple experiment. If the heart cannot dilate and its output per beat is fixed at a low level, then the only way the cardiac output per minute can increase is by the acceleration of the pulse rate. This being so, if the pulse rate be accelerated, for example, by atropine, one might expect the venous pressure to be reduced. This is in fact the case. When by the use of atropine the heart rate of a patient with constrictive pericarditis was elevated from 80 per minute to 120 per minute, the venous pressure fell to a significant degree. This I think bears out the theoretical concepts which have been so ably presented here.

Dr. Beck.—I have nothing further to say. I fully agree with Dr. Burwell's point of view as to the common source of the compression. It usually is over the entire heart, in my experience at least, and I think it is important for the surgeon to determine where the compressing agent is performing most of its compression. It usually is, but it may not always be, generalized over the ventricles. We have produced experiments in which the chief compression was over the right auricle. It is necessary for the surgeon to know exactly where the compression agent is functioning most, because in certain cases the surgical course is to the right of the sternum and not to the left, and, if you go in to the left of the sternum and find the right auricle compressed by a thick scar which has to be taken away to get exposure, you have to use a bilateral approach, including an approach on the right side of the sternum, which adds to the magnitude of the operation. I have done a few operations from the right side because we wanted to have a good exposure of the right auricle and right ventricle.

Discussion of the paper, "Fainting Attacks Resulting From Hypersensitive Carotid Sinus Reflexes," by Dr. Smith.

Dr. William J. Kerr, San Francisco, Calif.—We had one of the most striking examples of this sensitive reflex in San Francisco not long ago. Dr. John Musser was giving a dinner lecture on coronary occlusion, and one of our older, more obese

doctors who had not worn his dinner jacket for perhaps two or three years, came to this dinner and his collar was much too tight. He had a most remarkable attack which suggested an Adams-Stokes syndrome.

Dr. Soma Weiss, Boston, Mass.—Probably the most important and interesting part of the problem is presented by the group that we have studied in recent years, one that we named the "cerebral type." In this group, one finds syncope and convulsions, in spite of the fact that there is no cardiac slowing and no fall in the blood pressure. This group was described clinically by the English neurologist, Gowers, who considered these problems as being borderline between epilepsy and syncope. In this group, apparently the hyperactive carotid sinus reflex impulses produced inhibitions in certain vegetative centers. At least, that is the only conclusion that we can draw because the systemic blood flow, as well as the blood flow through the brain, remains normal.

To us, in addition to the practical points brought out by Dr. Smith, the most important aspect of the problem was that here is given an opportunity to study unconsciousness under controlled conditions. We have made various assumptions, in the past, as to the cause of unconsciousness and convulsions in human beings; but from the observations that we have made as to the physiology of unconsciousness, we can conclude that in man unconsciousness is caused by a number of different mechanisms, and among these mechanisms cerebral anoxia is only one. Nervous impulses and other factors play an equally important and probably a more important rôle.

Dr. John P. Anderson, Cleveland, Ohio.—I have observed unconscious attacks to follow carotid sinus pressure in some patients but in others have noticed no response.

In some instances the attacks followed pressure on the eyeball and in some patients, merely holding their breath would induce an attack. Some of them had their attacks at night when they would empty their bladders.

I should like to ask Dr. Smith if he thinks there is anything specific about the carotid sinus pressure.

Dr. Harry L. Smith, Rochester, Minn.—I am unable to answer this question positively, but in my experience there was not a constant correlation between the changes in respiration and heart rate and the syncopal attacks. Quite often, in the induced attacks, we did get rather striking changes in respiration. The most important changes noted were deep and labored respirations. These usually came on early, but in the induced attacks the patient might not lose consciousness, and there might be very few or no changes in the cardiac rate. In other words, there was no constant and definite correlation between the changes in respiration and heart rate and the syncopal attacks.

In answer to the second question—I have not induced attacks by making pressure over the eyeball. I would advise strongly against this practice as I do not think it is wise to make firm or continued pressure over the eyeball to induce attacks. The eye is a very delicate organ, and definite damage to the eyeball might result from the procedure.

Discussion of the paper, "The Use of Quinidine Sulphate Intravenously in Ventricular Tachycardia," by Dr. Hepburn and Dr. Rykert.

Dr. Paul D. White, Boston, Mass.—This is a method of treatment that has certainly not been used much. We should all have it in mind when we encounter similar cases, for occasionally it may be life-saving.

Discussion of the paper, "The Precipitating Causes of Congestive Heart Failure," by Dr. Sodeman and Dr. Burch.

Dr. C. Sidney Burwell, Boston, Mass.—I should like to draw one more moral from this interesting paper of Dr. Sodeman and Dr. Burch. This moral concerns the relation of the precipitating causes of heart failure to the management of patients with asymptomatic heart disease. The events which have, in the patients described by these authors, precipitated the onset of symptoms of heart disease have been in general events which increased the work of the heart. What is much more important, they have been, on the whole, events which are under a considerable degree of control on the part of the patient and his physician. The object of the treatment of heart disease is the prolongation of effective life. This being so, the adequate understanding and control by the physician of these precipitating causes is one of the most important things that can be carried out in dealing with the great group of people who have heart disease, but who have not yet developed heart failure. In these people, the problem is not that of the treatment of heart failure or cardiac pain, but the postponement of the onset of heart failure. This postponement is influenced more by the control of precipitating causes than by any other single factor except the advance of the underlying causative disease.

Dr. Louis F. Bishop, Jr., New York, N. Y.—I should like to ask what type of exercise was noted among the precipitating causes.

Dr. Sodeman.—Exercise in these patients varied, of course, and was usually the patient's work or some unusual activity which was carried out by the patient.

I wish to thank Dr. Burwell for his comments.

Discussion of the paper, "A Clinical Study of a Preparation of Squill (Urginin) in the Treatment of Myocardial Insufficiency," Dr. Chamberlain and Dr. Levy.

Dr. William D. Stroud, Philadelphia, Pa.—For the past year the concern manufacturing urginin has asked us at the Pennsylvania Hospital to try this drug in the heart clinic, and our reply has always been that since Dr. White and Dr. Marvin studied these other preparations similar to digitalis and had come to the conclusion that there was nothing they could do that digitalis could not do, that was the law and should stand.

But finally, having studied these digitalis preparations for the last six years, we felt we had a series of cases which warranted comparison, so Dr. Vander Veer and Dr. Dominick for the last few months have been transferring a number of these patients who have been taking various digitalis preparations for the last six years to urginin. I hesitate to discuss Dr. Chamberlain's and Dr. Levy's paper, since we have not come to definite conclusions which we can prove statistically, so this discussion must be taken with reservations.

I am just a little fearful that you may all go away from this meeting, after the summary which Dr. Chamberlain read, and shift your patients, now taking digitalis, to urginin. I urge you not to do this too precipitously since our impression is that this drug is not as universally potent in its action on patients with auricular fibrillation, whom we have been following for these past few years while taking various digitalis preparations.

I should like to ask Dr. Chamberlain if he feels there are many patients who cannot maintain their maximum circulatory efficiency on digitalis without developing toxic symptoms. In a group of such patients who cannot maintain circulatory efficiency without giving sufficient digitalis to give toxic symptoms, are there many who, transferred to an equivalent amount of urginin, will not develop

toxic symptoms? In other words, are there many patients with cardiovascular disease and borderline failure, who can take urginin without toxic symptoms, but will develop toxic symptoms when given an equivalent amount of digitalis.

Dr. James G. Carr, Evanston, Ill.—We worked with this preparation at the County Hospital and at the Evanston Hospital over a period of some four or five years before we offered anything for publication. Our detailed work is not so good as the work that has been presented here this afternoon, but we were convinced as a result of our work that a certain number of individuals who take digitalis with difficulty can be well controlled with the use of urginin.

Three cases which I followed over a period of some years come to my mind now. All of these patients were unable for one reason or another to take digitalis. Whether it was because they thought they could not take digitalis I am unable to say, but I do know that the cases had been given up by the physicians in charge and we were allowed to try the scillonin, under which name the drug was known at the time. Of these three patients, two are still living after seven and six years, respectively, following the first dose of the urginin preparation. We do not believe that the drug differs in any particular way from digitalis. It is of no greater value to the patient than is digitalis if the patient can take digitalis with comfort.

We found we could give to patients who had not taken any digitalis preparation within the last two weeks, from 8 to 12 mg. within four days without producing intoxication. The daily maintenance dose is 0.5 mg. or less. In one respect our results differed from those reported by Dr. Chamberlain and Dr. Levy. Our experience led us to believe that ectopic beats are usually the first sign of intoxication. We felt after we had worked with the drug for some time that patients who began to complain of nausea should have the drug withdrawn promptly as such patients were likely to develop rather pronounced signs of intoxication if the drug was continued.

On the basis of a considerable experience, 104 courses in 85 patients if I remember correctly, I believe that this drug is of value, not because it is better than digitalis, but because a certain number of people find it difficult to take enough digitalis to restore compensation.

Dr. Soma Weiss, Boston, Mass.—I would like to recall that, in spite of the fact that a number of digitalis preparations have been introduced in therapy during the last twenty years, so far it has not been proved that any of these preparations is, from a clinical point of view, superior to digitalis leaf itself.

If we remember that all digitalis bodies are quantitatively synergistic with each other, and if we further remember that the therapeutic effect depends on cardiac toxicity (cat unit), on the one hand, and on the persistence of action (rate of elimination) of these digitalis preparations on the other hand, plus the degree and type of failure of the circulation, then it will become clear that the variation in the clinical response to digitalis preparations depends more on these factors than on the specific pharmacological characteristics of the preparation itself.

In other words, this very interesting and valuable contribution has shown that urginin acts like digitalis. It did not show, and as I understand it is not claimed, that it is a better agent than digitalis. Whether in the few instances where no untoward manifestations occurred this was due to the fact that urginin, in contrast to digitalis, does not cause or induces less nausea or vomiting, or whether as a result of the difference in the persistence of action of the two drugs, relatively smaller doses of urginin were given, in spite of the fact that the doses expressed in cat units were similar, it is difficult to say.

So my conclusion is that as long as it is not definitely established that a preparation is better than digitalis, and as long as we know a great deal about digitalis purpurea, it is wiser to stick to that simple preparation rather than to use a drug which is more expensive and less well understood.

Dr. Chamberlain.—It is difficult to compare the action of two drugs in a condition so variable in its course as congestive heart failure. Our observations indicate that urginin shows no superiority over digitalis with respect to its action in cardiac insufficiency. The place to use urginin, at least for the present, is in those patients who, because of idiosyncrasy or prejudice, are unable to take digitalis without discomfort. There were some ten patients in our series who supposedly had an idiosyncrasy to digitalis and by whom urginin was well taken. Later, on administering digitalis, either by injection or in a form which they did not recognize, their idiosyncrasy was found to be imaginary. There were two patients, however, who definitely could not tolerate digitalis and who were able to take urginin without unpleasant effects.

Department of Reviews and Abstracts

Selected Abstracts

Radnai, P., and Mosoyni, L.: Vasoconstrictor Pulmonary-Coronary Reflex. Ztschr. f. d. ges. exper. Med. **98**: 651, 1936.

Injection of starch suspensions in the ear veins of the rabbit causes only pulmonary emboli. None appears in the heart. Yet five to six minutes after such injections the electrocardiogram shows evidence of acute coronary closure. This is interpreted as a reflex closure from the lungs. When the vagi are sectioned, these electrocardiographic findings are absent. The vagi are, the authors conclude, the path of the afferent pulmonary fibers and efferent coronary fibers. Both atropine and amyl nitrite prevent this reflex from occurring. The application of these results to the clinical understanding of pulmonary embolism and angina pectoris is emphasized.

L. N. K.

Wahren, H.: O_2 Consumption in Postoperative Shock. Ztschr. f. Kreislaufforsch. **29**: 149, 1937.

O_2 consumption is decreased in the entire animal (cats) following shock, and O_2 tension in a subcutaneous gas bubble decreases at the same time that CO_2 increases.

L. N. K.

de Carrasco, O., and Zaeper, G.: The O_2 Dissociation Curve of the Blood and Circulation. Ztschr. f. Kreislaufforsch. **29**: 157, 1937.

The authors correlated O_2 dissociation curve of blood with O_2 utilization. It is pointed out that the normal O_2 dissociation curve is such as to make O_2 exchange inadequate during muscular work and in abnormalities of the circulation. A shift of the curve to the right occurs in these conditions and permits an adequate O_2 exchange with the tissues. This is due to a change in the state of the hemoglobin, presumably the result of CO_2 excess and pH change in the blood.

L. N. K.

Lederer, E.: Capillary Circulation Studies. I. Fundamentals, Methods. Arch. f. exper. Path. u. Pharmakol. **182**: 363, 1936.

The circulation time in 0.4 limbus capillaries averaged 1.6 to 2.4 seconds in 12 healthy children. Readings repeated at a single sitting varied from 0.2 to 0.8 second which represents the physiological range of changes. The repeated readings over several weeks showed no greater fluctuations than in successive readings at one sitting.

L. N. K.

Ehrström, M. C.: Metabolism of Blood and Urobilinuria in Insufficiency of the Heart. Acta med. Skandinav. **88**: 517, 1936.

Ten cases of heart failure were studied. A reversible reticulocytosis during failure was found. This is associated with an increased total urobilin production. The urobilinemia is paralleled by a urobilinuria. Hemolysis is the cause of this change in pigment metabolism in heart failure.

L. N. K.

Faleiro, A.: "Exercise Test" in the Electrocardiographic Diagnosis of Angina Pectoris. Deutsches Arch. f. klin. Med. **179**: 238, 1936.

In this presentation, 60 patients with typical stenocardia and 250 patients with a questionable diagnosis were studied. A test was considered positive when a depression of 1 mm. of S-T in Lead I (and II) occurred, when T became flattened or inverted or when S-T became abnormally elevated following exercise. Thirty-two per cent of the cases with definite angina showed this positive exercise test. None of the cases with a questionable diagnosis gave a positive exercise test.

L. N. K.

Brandt, W., and Reindell, H.: The Electrocardiogram of the Isolated Frog Heart Under Influence of Light and Heavy Water. Klin. Wchnschr. **15**: 260, 1936.

Studies show that Ringer solution having less than 5 per cent of dueterium oxide has no effect whereas concentration of this substance of 10 to 20 per cent has a measurable effect, and concentrations of 50 per cent have a marked effect on perfused frog hearts. This is manifest in a decreased amplitude, prolonged A-V conduction time, prolonged systole, and a decrease in the rate of beating. Total A-V block may appear. These changes can be reversed by substituting ordinary Ringer solution. Apparently, the dueterium oxide acts to show metabolic processes.

L. N. K.

Kahlstorf, A.: Heart Size in Paroxysmal Tachycardia. Klin. Wchnschr. **15**: 1028, 1936.

A case of paroxysmal auricular flutter with 1 to 1 conduction and auricular rate of 280 was observed in the roentgenkymograph two hours after the onset of the paroxysm. Enlargement of the heart, decrease in size of the blood vessel shadow, and venous stasis were found. It is interesting that the kymograph gave an idea of the mechanism in this case. The author suggests the use of the roentgenkymograph to determine the origin of paroxysmal pacemakers.

L. N. K.

Rihl, J., and Spiegl, E.: Concerning Interference of Two Excitation Waves in the Ventricle. Med. Klin. **32**: 841, 1936.

The electrocardiographic appearance of a beat resulting from fusion of the impulse from a late diastolic ventricular extrasystole and impulse transmitted through from the sinus node is described.

L. N. K.

Eckey, P.: Electrocardiographic Changes in So-Called Cor Nervosum. München. med. Wchnschr. **83**: 1051, 1936.

The author concludes from his studies that the electrocardiogram sometimes may be misleading in differentiating organic heart disease from the so-called functional heart disorders.

L. N. K.

Herzog, E., and Rodriguez, H.: Involvement of the Myocardium in Exanthemata (Myocarditis Exanthematica). Beitr. z. path. Anat. u. allg. Path. **96:** 431, 1936.

In exanthemata only enlargement of the left ventricle occurs grossly, but microscopically 97 per cent shows disseminated diffuse interstitial myocarditis with perivascular (capillary and precapillary) cellular invasion consisting of fibroblasts, plasma cells, lymphocytes, and polymorphonuclear leucocytes. The capillary walls are swollen and inflamed. Leucocytes occur early in the disease and lymphocytes later. Myocardial degeneration is rare. Involvement of the conduction system was found 3 times in 13 cases examined. This consisted of leucocytic infiltration and fatty degeneration of some fibers of the left bundle. The electrocardiographic changes resemble those seen in diphtheria.

L. N. K.

Oille, John A.: Differential Diagnosis of Pain in the Chest. Canad. M. A. J. **37:** 209, 1937.

The author discusses the differential diagnosis of pain in the chest as a symptom of cardiac disease. The observations are based on a group of 225 patients selected from a large group of 600 cases seen in practice. There is a full description of the various features of cardiac pain, especially as it relates to a diagnosis of coronary thrombosis. The article is unusually interesting from a clinical standpoint in interpreting this important symptom.

H. McC.

Gouley, Benjamin A., McMillan, Thomas M., and Bellet, Samuel: Idiopathic Myocardial Degeneration Associated With Pregnancy and Especially the Puerperium. Am. J. M. Sc. **194:** 185, 1937.

A clinical study was made of seven women having cardiac decompensation in the puerperium. Four of these patients died, and at necropsy showed a myocardial degeneration differing from the lesions ordinarily associated with the current classification of heart disease.

The coronary arteries were normal and there was no evidence of coronary occlusion in the living patients.

Death occurred in three cases following embolism, which had its origin on the endocardial surface of degenerated heart muscle. No other proven source of embolism was found.

Pulmonary and cerebral embolism were notable. Slight patency of the foramen ovale, apparently due to recent pressure changes within the right auricle and allowing the passage of a pencil, was present in one instance. No patency was demonstrated in the three remaining cases.

AUTHOR.

Friedman, R.: Effect of Valvular Deformities on the Duration of Life. Ztschr. f. klin. Med. **130:** 382, 1936.

Statistical analysis is presented of rheumatic hearts in Vienna—a total of 1,164 cases. It was found that 67.5 per cent had the first rheumatic manifestations in the first two decades of life. Mitral valve and combined valve involvement were commonest. A combination of mitral stenosis and insufficiency was the rarest of the mitral defects. Eighty-three and five-tenths per cent of the patients died because of valve defects or their sequelae. The death rate increased until the fifth decade. Heart size plays an important rôle in prognosis. The work is in accord with that in American literature.

L. N. K.

Levine, Harry B., and White, Paul D.: Pulmonary Infarction Complicating Severe Disease of the Mitral Valve. Arch. Int. Med. 60: 39, 1937.

We report here 5 cases of severe disease of the mitral valve with congestive failure having as a fatal complication pulmonary infarction without any clinical syndrome of sudden vascular collapse or any similar episode. Autopsy was performed in each case.

Analysis of the incidence of this complication in a series of 52 cases of mitral stenosis noted in 2,500 records of autopsies at the Massachusetts General Hospital showed that pulmonary infarction occurred in 61 per cent of 23 cases in which there was congestive failure and in only 7 per cent of the cases in which congestive failure was not present. In a comparative group of 82 cases of hypertension noted in the records of 1,400 autopsies at the Massachusetts General Hospital, there were 39 cases of congestive failure, in 21 per cent of which there was pulmonary infarction.

Pulmonary infarction complicating severe disease of the mitral valve with congestive failure is not uncommon. This condition is sometimes difficult to diagnose; it makes treatment of the congestion very difficult, and it renders the prognosis grave.

AUTHOR.

Greishaber, H.: Situs Inversus of Abdominal Organs With Congenital Heart and Right Sided Aortic Arch. Schweiz. med. Wchnschr. 52: 1307, 1936.

In spite of right-sided aortic arch and situs inversus of the abdominal organs, there was no dextrocardia. The heart had a septal defect. The low position of the left side of the diaphragm in this case despite the left-sided position of the liver indicates that this is caused by the heart. The liver does not, therefore, normally elevate the right diaphragm. The case had a mirror image of normal in Lead I in spite of the absence of dextrocardia.

L. N. K.

Borgard, W.: Congenital Anomalies of the Aorta. Ztschr. f. Kreislaufforsch. 29: 216, 1937.

A case report is presented of stenosis of the aortic arch between the origins of the left carotid and the left subclavian arteries, with typical x-ray findings and an abnormal electrocardiogram with left ventricular preponderance. The diagnosis is made on these findings plus the clinical signs of absence of pulsations in the lower extremities of a relatively smaller pulse in the left than the right radial, of the presence of collaterals on the right upper chest posteriorly, of a systolic murmur over the pericardium, and of cardiac enlargement.

L. N. K.

Messeloff, Charles R., and Pomerantz, Anne: A Study of Lead IV in Normal Children and in Ambulatory Children With Cardiac Disease. Am. J. Dis. Child. 53: 1485, 1937.

Lead IV in the electrocardiograms of children is characterized by a marked variability in the form and in the direction of its several compounds.

Upright, diphasic, and iso-electric, as well as negative T-waves are normal findings in the tracings of children.

In the present series of tracings for ambulatory children with heart disease Lead IV supplied no information which was not secured from the three standard leads.

This study provides no justification for the routine use of Lead IV for ambulatory children with heart disease.

AUTHOR.

Wilson, Robert, Jr.: Studies in Syphilitic Cardiovascular Disease. Am. J. M. Sc. **194:** 178, 1937.

Two hundred and eleven cases of syphilitic aortitis, proven at autopsy, have been analyzed with regard to presenting symptoms. In practically every case in which cardiac or respiratory symptoms were present, they have been shown to be due to some factor other than uncomplicated syphilitic aortitis—either to an extension or complication of the syphilitic process or to some coexisting disease. It is concluded that uncomplicated syphilitic aortitis is an asymptomatic condition, and that no criteria dependent upon symptoms are reliable in making an early diagnosis.

AUTHOR.

Cossio, P., Vivoli, D., and Caul, H.: Syphilis of the Interventricular Septum and Ventricular Tachycardia. Am. J. M. Sc. **194:** 369, 1937.

This report deals with a case of ventricular tachycardia caused by a syphilitic lesion of the interventricular septum.

It was a typical attack of ventricular tachycardia due to infarction of the interventricular septum.

The lesion was of the sclerogummatous type with endocoronaritis, and *Treponema pallidum* was found in it.

This observation, as far as we know, is the first of its kind in medical literature, and shows that a syphilitic lesion of the septum is able to produce an attack of ventricular tachycardia. In a case of prolonged attack of ventricular tachycardia, provided that the Wassermann and Kahn tests are positive, we must not only suspect infarction of the septum of the ordinary type, but also one of syphilitic etiology.

AUTHOR.

Potthoff, F.: Tuberculosis and Heart Size. A Study of 600 X-rays of Men With Tuberculosis. Beitr. z. klin. d. Tuberk. **88:** 187, 1936.

A large number of tuberculous patients show definitely smaller hearts than normal. Only in severe tuberculosis does brown atrophy occur. The small hearts are therefore hypoplastic and may be associated with the patient's constitutional makeup. In the present series, 88 per cent had hearts smaller than normal (the normal series used being that reported by Hammer).

L. N. K.

Weber, H.: Early Diagnosis of Arteriosclerosis. Med. Welt. **10:** 928, 1936.

The most common site of early arteriosclerosis is in the coronary arteries. This may give evidence of heart failure in the form of tachycardia and shortness of breath. It is not easy to demonstrate this arteriosclerosis by roentgenogram. Consequently many years may elapse before the arteriosclerosis is diagnosed clinically.

L. N. K.

Gerstner, H.: Action of Electrical Currents Upon the Blood Pressure. Arch. f. exper. Path. u. Pharmakol. **185:** 184, 1937.

Direct current and alternating current of various frequencies and strengths were applied to anesthetized dogs. Arterial blood pressure and pressure within the abdominal cavity, used as an index of general muscular tension, were recorded simultaneously. He was not able to demonstrate narrowing of the peripheral vessels apart from that due to tension of tetanized muscles. Gerstner found that, as

current was increased, first a rise in blood pressure occurred which appeared to be simultaneous with onset of muscular contraction. Then due to marked slowing of the heart, ending in final stoppage in diastole, occasionally to ventricular fibrillation, a sharp fall occurred. When stimulation with the strength of the alternating current constant but with gradually decreasing frequency of oscillation was used, observable effects on blood pressure or striate muscle did not occur until the frequency fell to 2,000 cycles per second. Arterial pressure then rose but not until 50 cycles per second was reached did the heart stop and fall in pressure occur.

J. M. S.

Neuhaus, F.: Relation of Adrenal Adenoma in Hypertension. Beitr. z. path. Anat. u. z. allg. Path. **97:** 213, 1936.

Seven hundred adrenals were examined. The adenomas were twice as common in hypertensive persons as in those with normal blood pressure. Adenoma of the adrenal is considered a sequel and not a cause of hypertension.

L. N. K.

Singer, R.: New Observations on the Circulation of the Lower Extremities. I. Arterial Pressure in the Limb Vessels. Wien. klin. Wchnschr. **49:** 44, 1936.

Changing from lying to sitting or standing position elevates the blood pressure in the lower extremity. This is attributed to a hydrostatic pressure change. Simply changing the position of the leg (or arm) leads to similar fluctuations of pressure.

L. N. K.

Apperly, Frank L., and Cary, M. Katharine: Arterial Hypertension. The Site and Significance of the High Chloride Content of the Blood. Am. J. M. Sc. **194:** 352, 1937.

In a study to determine the site of increased blood chloride in patients with arterial hypertension, and if possible its significance, it was found:

1. The increased blood chloride is wholly confined to the red cells.
2. This increased cell chloride is not the result of acidemia, since pH and erythrocytic volume-index showed no significant deviations from the normal.

AUTHOR.

Zetter: The Action of Drugs Upon the Permeability of Arteries. Arch. f. exper. Path. u. Pharmakol. **185:** 141, 1937.

Estimations of the permeability of carotid arteries of swine and a few human femoral arteries were made by the method of Lange. This method consists of placing a 6 to 10 cm. length of artery, tied at each end to a cannula and connected to a manometer, in a small bath (20 c.c. capacity) at body temperature. The lumen of the artery and the surrounding bath are filled with solutions or suspensions different in nature and the passage of material in or out of the artery observed. The intactness of the arteries, chiefly the absence of minute branches, was insured by discarding those which were permeable to congo red, normal arteries having been shown earlier by Lange to be impermeable to this dye. The influence of the addition of drugs either to the fluid surrounding or contained in arteries upon their permeability to fluorescin and napthol yellow was then tested. Zetter found that nitrites, and either purine or mercurial diuretics increase, and that calcium and nicotine decrease permeability of the arterial walls. The forcefulness of the conclusions are, however, somewhat vitiated by the fact that quantitative measure-

ments seem not to have been possible even though photometric estimations were made of the content of dyes in the bathing fluids. The author merely gives statements that permeability is slightly or markedly increased or decreased, or unchanged. Changes in diameter of lumen appeared not to be related to changes in permeability.

J. M. S.

Goedel, A.: Primary Sarcoma of the Pulmonary Artery. Frankfurt. Ztschr. f. Path. **49**: 1, 1936.

A case is reported in a forty-seven-year-old man, the fifth in the literature, of a sarcoma of the pulmonary artery. All cases were diagnosed postmortem. In this case the tumor masses were in the lumina of the vessels, resembling emboli or thrombi grossly. The diagnosis was apparent on histological examination. Only in two cases was growth apparent outside the vessel wall. Metastases were present in the lungs and right heart cavity.

L. N. K.

Perlow, Samuel, and Bloch, Leon: Impending Gangrene of the Feet Due to Ergotamine Tartrate. J. A. M. A. **109**: 27, 1937.

In a case of ergotamine tartrate poisoning with impending gangrene of the feet, an apparently complete cure was brought about by the use of papaverine hydrochloride. The patient had received 3.5 mg. of ergotamine tartrate in divided doses within eleven days. On the last day of this medication there was severe pain in the toes and evidences of arterial insufficiency. Seven hypodermic injections of gr. ¼ of morphine were required in twenty-four hours to afford relief of the pain. There was no pulsation in dorsalis pedis or posterior tibial arteries. A diagnosis of spasm and a possibly beginning occlusion of the arteries of both feet was made. Two days later, he was given gr. ½ of papaverine hydrochloride intravenously, and gr. ½ twice the next day, following which the pain was relieved and there was great improvement in the condition of the feet. Arterial pulsations returned. On each of the next two days, gr. ½ of papaverine hydrocholoride was given by mouth. Suction and pressure was used toward the end of the papaverine therapy. Within these several days, all signs and symptoms of occlusion disappeared.

H. M.

Singer, R.: New Observations on the Circulation of the Lower Extremities. II. Normal and Pathological Circulatory Changes in the Limb Veins. Wien. klin. Wchnschr. **49**: 366, 1936.

The author determines the emptying ability from the vein as follows: the artery is compressed with the limb horizontal, and it is observed that following lowering of the limb 45° below horizontal the vein fills from above, whereas no filling occurs on returning the limb to the horizontal position following elevation of the limb 45°. The state of the vein wall is determined by stretching the vein after stopping the flow from the capillaries. An abnormal vein rigidity is indicated when the vessel remains elevated. The rate of flow into the vein is determined by the refilling time on release of the peripheral compression point of a stretch of vein emptied between compression points.

L. N. K.

Singer, R.: New Observations on the Circulation of the Lower Extremities. III. Clinical Observations. Wien. klin. Wchnschr. **49**: 871, 1936.

The blood pressure in the lower extremity in disease sinks to the level in the upper extremity, especially when there is endarteritis. This blood pressure difference

can be used as an index of therapeutic efficacy. Insufficiency of the right heart and early venous thrombosis are manifested by prolonged emptying time of the vein following elevation of the limb 45° from the horizontal. Normally this value is two to six seconds. The refilling time on return to horizontal (normal value five to twenty seconds) gives an index of the state of arterial flow. A refilling time of fifty seconds is to be taken as of serious moment.

L. N. K.

Rautmann, H.: Roentgenological Studies of the Heart in Athletes. Med. Welt. **10**: 1097, 1936.

A marked dilation of the heart can occur on overexertion without subjective symptoms or cardiac acceleration. This is a good way of checking for overexertion.

L. N. K.

Parade, G. W.: Heart Disease and Athletics. Med. Welt. **10**: 1101, 1936.

No limitation was noted in the ability to participate in sports in many patients with valvular disease. In fact, regulated exercise will improve the condition by leading to bradycardia, but lack of care in such activity can lead to heart failure. Only myocardial damage is a contraindication to athletics. Arrhythmias like extrasystoles and auricular fibrillation per se are no contraindication for such activities. A case is cited of a skier who had heart block with dropped beats and who had no ill effects from his activity. Nevertheless, each case should be judged individually.

L. N. K.

Grundig, J.: The Management of Congestive Catarrh and Cardiac Asthma in a Spa. Balneologe **3**: 354, 1936.

Those subject to cardiac asthma due to left heart failure should not be sent to a spa. However, patients with chronic congestive failure such as occurs in mitral stenosis do well at spas. The use of CO_2 baths, O_2 inhalation, and venesection are recommended as is also nitrites or nitrites and digitalis, sedatives, and narcotics.

L. N. K.

Parade, G. W.: Heart Disturbances Following Cold Baths. Balneologe **3**: 406, 1936.

Baths of 18 to 20° were used on 50 normal subjects. The following abnormal rhythms were found following the use of the cold bath: one instance of A-V dissociation, several of auricular paroxysmal tachycardia, and sinus arrhythmia (nonphasic).

L. N. K.

Crassusi: Clinical Use of Adenis Vernalis (Adonigen). Deutsche med. Wchnschr. **62**: 1613, 1936.

This acts as a sedative to the ectopic pacemakers of the heart. It was used orally and rectally in 57 cases. The indications are similar to those of digitalis. Twenty to thirty drops of adonigen may be used three times a day or one or two tablets orally or one or two suppositories daily.

L. N. K.